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(54) Title: HIGH EFFICIENCY GENE TRANSFER AND EXPRESSION IN MAMMALIAN CELLS BY A MULTIPLE TRANSFECTION PROCEDURE OF MAR SEQUENCES

(57) Abstract: The present invention relates to purified and isolated DNA sequences having protein production increasing activity and more specifically to the use of matrix attachment regions (MARs) for increasing protein production activity in a eukaryotic cell. Also disclosed is a method for the identification of said active regions, in particular MAR nucleotide sequences, and the use of these characterized active MAR sequences in a new multiple transfection method.

# HIGH EFFICIENCY GENE TRANSFER AND EXPRESSION IN MAMMALIAN CELLS BY A MULTIPLE TRANSFECTION PROCEDURE OF MAR SEQUENCES

#### FIELD OF THE INVENTION

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The present invention relates to purified and isolated DNA sequences having protein production increasing activity and more specifically to the use of matrix attachment regions (MARs) for increasing protein production activity in a eukaryotic cell. Also disclosed is a method for the identification of said active regions, in particular MAR nucleotide sequences, and the use of these characterized active MAR sequences in a new multiple transfection method.

### **BACKGROUND OF THE INVENTION**

Nowadays, the model of loop domain organization of eukaryotic chromosomes is well accepted (Boulikas T, "Nature of DNA sequences at the attachment regions of genes to the nuclear matrix", *J. Cell Biochem.*, 52:14-22, 1993). According to this model chromatin is organized in loops that span 50-100 kb attached to the nuclear matrix, a proteinaceous network made up of RNPs and other nonhistone proteins (Bode J, Stengert-Iber M, Kay V, Schalke T and Dietz-Pfeilstetter A, *Crit. Rev. Euk. Gene Exp.*, 6:115-138, 1996).

The DNA regions attached to the nuclear matrix are termed SAR or MAR for respectively scaffold (during metaphase) or matrix (interphase) attachment regions (Hart C and Laemmli U (1998), "Facilitation of chromatin dynamics by SARs" *Curr Opin Genet Dev* 8, 519-525.)

As such, these regions may define boundaries of independent chromatin domains, such that only the encompassing cis-regulatory elements control the expression of the genes within the domain.

However, their ability to fully shield a chromosomal locus from nearby chromatin elements, and thus confer position-independent gene expression, has not been seen in stably transfected cells (Poljak L, Seum C, Mattioni T and Laemmli U. (1994) "SARs stimulate but do not confer position independent gene expression", *Nucleic Acids Res* 22, 4386-4394). On the other hand, MAR (or S/MAR) sequences have been shown to interact with enhancers to increase local chromatin accessibility (Jenuwein T, Forrester W, Fernandez-Herrero L, Laible G, Dull M, and Grosschedl R. (1997) "Extension of chromatin accessibility by nuclear matrix attachment regions" *Nature* 385, 269-272).

Specifically, MAR elements can enhance expression of heterologous genes in cell culture lines (Kalos M and Fournier R (1995) "Position-independent transgene expression mediated by boundary elements from the apolipoprotein B chromatin domain" *Mol Cell Biol* 15,198-207), transgenic mice (Castilla J, Pintado B, Sola, I, Sanchez-Morgado J, and Enjuanes L (1998) "Engineering passive immunity in

transgenic mice secreting virus-neutralizing antibodies in milk" *Nat Biotechnol* 16, 349-354) and plants (Allen G, Hall GJ, Michalowski S, Newman W, Spiker S, Weissinger A, and Thompson W (1996), "High-level transgene expression in plant cells: effects of a strong scaffold attachment region from tobacco" *Plant Cell* 8, 899-913). The utility of MAR sequences for developing improved vectors for gene therapy is also recognized (Agarwal M, Austin T, Morel F, Chen J, Bohnlein E, and Playec I (1998), "Scaffold

(Agarwal M, Austin T, Morel F, Chen J, Bohnlein E, and Plavec I (1998), "Scaffold attachment region-mediated enhancement of retroviral vector expression in primary T

cells" J Virol 72, 3720-3728).

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Recently, it has been shown thatchromatin-structure modifying sequences including MARs, as exemplified by the chicken lysozyme 5' MAR is able to significantly enhance reporter expression in pools of stable Chinese Hamster Ovary (CHO) cells (Zahn-Zabal M, et al., "Development of stable cell lines for production or regulated expression using matrix attachment regions" J Biotechnol, 2001, 87(1): p. 29-42). This property was used to increase the proportion of high-producing clones, thus reducing the number of clones that need to be screened. These benefits have been observed both for constructs with MARs flanking the transgene expression cassette, as well as when constructs are cotransfected with the MAR on a separate plasmid. However, expression levels upon cotransfection with MARs were not as high as those observed for a construct in which two MARs delimit the transgene expression unit. A third and preferable process was shown to be the transfection of transgenes with MARs both linked to the transgene and on a separate plasmid (Girod et al., submitted for publication). However, one persisting limitation of this technique is the quantity of DNA that can be transfected per cell. Many multiples transfection protocols have been developed in order to achieve a high transfection efficiency to characterize the function of genes of interest. The protocol applied by Yamamoto et al, 1999 ("High efficiency gene transfer by multiple transfection protocol", Histochem. J. 31(4), 241-243) leads to a transfection efficiency of about 80 % after 5 transfections events, whereas the conventional transfection protocol only achieved a rate of <40%. While this technique may be useful when one wishes to increase the proportion of expressing cells, it does not lead to cells with a higher intrinsic productivity. Therefore, it cannot be used to generate high producer monoclonal cell lines. Hence, the previously described technique has two major drawbacks:

- this technique does not generate a homogenous population of transfected cells, since it cannot favour the integration of further gene copy, nor does it direct the transgenes to favorable chromosomal loci,
- the use of the same selectable marker in multiple transfection events does not permit the selection of doubly or triply transfected cells.

In patent application WO02/074969, the utility of MARs for the development of stable eukaryotic cell lines has also been demonstrated. However, this application does not disclose neither any conserved homology for MAR DNA element nor any technique for predicting the ability for a DNA sequence to be a MAR sequence.

In fact no clear-cut MAR consensus sequence has been found (Boulikas T, "Nature of DNA sequences at the attachment regions of genes to the nuclear matrix", *J. Cell Biochem.*, 52:14-22, 1993) but evolutionarily, the structure of these sequences seem to be functionally conserved in eukaryotic genomes, since animal MARs can bind to plant nuclear scaffolds and vice versa (Mielke C, Kohwi Y, Kohwi-Shigematsu T and Bode J, "Hierarchical binding of DNA fragments derived from scaffold-attached regions: correlation of properties in vitro and function in vivo", *Biochemistry*, 29:7475-7485, 1990).

The identification of MARs by biochemical studies is a long and unpredictable process; various results can be obtained depending on the assay (Razin SV, "Functional architecture of chromosomal DNA domains", *Crit Rev Eukaryot Gene Expr.*, 6:247-269, 1996). Considering the huge number of expected MARs in a eukaryotic genome and the amount of sequences issued from genome projects, a tool able to filter potential MARS in order to perform targeted experiments would be greatly useful.

Currently two different predictive tools for MARs are available via the Internet. The fist one, MAR-Finder (http://futuresoft.org/MarFinder; Singh GB, Kramer JA and Krawetz SA, "Mathematical model to predict regions of chromatin attachment to the nuclear matrix", Nucleic Acid Research, 25:1419-1425, 1997) is based on set of patterns identified within several MARs and a statistical analysis of the co-occurrence of 5 these patterns. MAR-Finder predictions are dependent of the sequence context, meaning that predicted MARs depend on the context of the submitted sequence. The other predictive software, SMARTest (http://www.genomatix.de; Frisch M, Frech K, Klingenhoff A, Cartharius K, Liebich I and Werner T, "In silico prediction of scaffold/matrix attachment regions in large genomic sequences", Genome Research, 10 12:349-354, 2001), use weight-matrices derived from experimentally identified MARs. SMARTest is said to be suitable to perform large-scale analyses. But actually aside its relative poor specificity, the amount of hypothetical MARs rapidly gets huge when doing large scale analyses with it, and in having no way to increase its specificity to restrain the number of hypothetical MARs, SMARTest becomes almost useless to screen for 15 potent MARs form large DNA sequences. Some other softwares, not available via the Internet, also exists; they are based as well on the frequency of MAR motifs (MRS criterion; Van Drunen CM et al., "A bipartite sequence element associated with matrix/scaffold attachment regions", Nucleic Acids Res. 27:2924-2930, 1999), (ChrClass; Glazko GV et al., "Comparative study and 20 prediction of DNA fragments associated with various elements of the nuclear matrix". Biochim. Biophys. Acta, 1517:351-356, 2001) or based on the identification of sites of stress-induced DNA duplex (SIDD; Benham C and al., "Stress-induced duplex DNA destabilization in scaffold/matrix attachment regions", J. Mol. Biol., 274:181-196, 1997). However, their suitability to analyze complete genome sequences remains unknown. 25 and whether these tools may allow the identification of protein production-increasing sequences has not been reported.

Furthermore, due to the relatively poor specificity of these softwares (Frisch M, Frech K, Klingenhoff A, Cartharius K, Liebich I and Werner T, "In silico prediction of scaffold/matrix attachment regions in large genomic sequences", *Genome Research*, 12:349-354, 2001), the amount of hypothetical MARs identified in genomes rapidly gets unmanageable when doing large scale analyses, especially if most of these have no or poor activity in practice. Thus, having no way to increase prediction specificity to restrain the number of hypothetical MARs, many of the available programs become almost useless to identify potent genetic elements in view of efficiently increasing recombinant protein production.

Since all the above available predictive methods have some drawbacks that prevent large-scale analyses of genomes to identify reliably novel and potent MARs, the object of this invention is to 1) understand the functional features of MARs that allow improved recombinant protein expression; 2) get a new Bioinformatic tool compiling MAR structural features as a prediction of function, in order to 3) perform large scale analyses of genomes to identify novel and more potent MARs, and, finally 4) to demonstrate improved efficiency to increase the production of recombinant proteins from eukaryotic cells or organisms when using the newly identified MAR sequences.

#### **SUMMARY OF THE INVENTION**

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This object has been achieved by providing an improved and reliable method for the identification of DNA sequences having protein production increasing activity, in

particular MAR nucleotide sequences, and the use of these characterized active MAR sequences in a new multiple transfection method to increase the production of recombinant proteins in eukaryotic cells.

#### BRIEF DESCRIPTION OF THE FIGURES

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Fig. 1 shows the distribution plots of MARs and non-MARs sequences. Histograms are density plots (relative frequency divided by the bin width) relative to the score of the observed parameter. The density histogram for human MARs in the SMARt DB database is shown in black, while the density histogram for the human chromosome 22 are in grey.

Fig. 2 shows Scatterplots of the four different criteria used by SMAR Scan® and the AT-content with human MARs from SMARt DB.

Fig. 3 shows the distribution plots of MAR sequences by organism. MAR sequences from SMARt DB of other organisms were retrieved and analyzed. The MAR sequences density distributions for the mouse, the chicken, the sorghum bicolor and the human are plotted jointly.

Fig. 4 shows SMAR Scan® predictions on human chromosome 22 and on shuffled chromosome 22. Top plot: Average number of hits obtained by SMAR Scan® with five: rubbled, scrambled, shuffled within nonoverlapping windows of 10 bp, order 1 Markov chains model and with the native chromosome 22. Bottom plot: Average number of MARs predicted by SMAR Scan® in five: rubbled, scrambled, shuffled within nonoverlapping windows of 10 bp, order 1 Markov chains model and with the native chromosome 22.

Fig. 5 shows the dissection of the ability of the chicken lysozyme gene 5'-MAR to stimulate transgene expression in CHO-DG44 cells. Fragments B, K and F show the highest ability to stimulate transgene expression. The indicated relative strength of the elements was based on the number of high-expressor cells.

Fig. 6 shows the effect of serial-deletions of the 5'-end (upper part) and the 3'-end (lower part) of the 5'-MAR on the loss of ability to stimulate transgene expression. The transition from increased to decreased activity coincide with B-, K- and F-fragments.

Fig. 7 shows that portions of the F fragment significantly stimulate transgene expression. The F fragment regions indicated by the light grey arrow were multimerized, inserted in pGEGFP Control and transfected in CHO cells. The element that displays the highest activity is located in the central part of the element and corresponds to fragment FIII (black bar labelled minimal MAR). In addition, an enhancer activity is located in the 3'-flanking part of the FIII fragment (dark grey bar labelled MAR enhancer).

Fig. 8 shows a map of locations for various DNA sequence motifs within the *cLysMAR*. Fig. 8 (B) represents a Map of locations for various DNA sequence motifs within the cLysMAR. Vertical lines represent the position of the computer-predicted sites or sequence motifs along the 3034 base pairs of the cLysMAR and its active regions, as presented in Fig. 5. The putative transcription factor sites, (MEF2 05, Oct-1, USF-02, GATA, NFAT) for activators and (CDP, SATB1, CTCF, ARBP/MeCP2) for repressors of transcription, were identified using MatInspector (Genomatix), and CpG islands were identified with CPGPLOT. Motifs previously associated with MAR elements are labelled

in black and include CpG dinucleotides and CpG islands, unwinding motifs (AATATATT and AATATT), poly As and Ts, poly Gs and Cs, Drosophila topoisomerase II binding sites (GTNWAYATTNATTNATNNR) which had identity to the 6 bp core and High mobility group I (HMG-I/Y) protein binding sites. Other structural motifs include nucleosome-binding and nucleosome disfavouring sites and a motif thought to relieve the superhelical strand of DNA. Fig. 8(A) represents the comparison of the ability of portions of the cLysMAR to activate transcription with MAR prediction score profiles with MarFinder. The top diagram shows the MAR fragment activity as in Fig. 5, while the middle and bottom curves show MARFinder-predicted potential for MAR activity and for bent DNA structures respectively.

Fig. 9 shows the correlation of DNA physico-chemical properties with MAR activity. Fig. 9(A), represents the DNA melting temperature, double helix bending, major groove depth and minor groove width profiles of the 5'-MAR and were determined using the algorithms of Levitsky et al (Levitsky VG, Ponomarenko MP, Ponomarenko JV, Frolov AS, Kolchanov NA "Nucleosomal DNA property database", *Bioinformatics*, 15; 582592, 1999). The most active B, K and F fragments depicted at the top are as shown as in Figure 1. Fig. 9(B), represents the enlargement of the data presented in panel A to display the F fragment map aligned with the tracings corresponding to the melting temperature (top curve) and DNA bending (bottom curve). The position of the most active FIB fragment and protein binding site for specific transcription factors are as indicated.

Fig. 10 shows the distribution of putative transcription factor binding sites within the 5'-cLysMAR. Large arrows indicate the position of the CUE elements as identified with SMAR Scan®.

Fig. 11 shows the scheme of assembly of various portions of the MAR. The indicated portions of the cLysMAR were amplified by PCR, introducing BgIII-BamHI linker elements at each extremity, and assembled to generate the depicted composite elements. For instance, the top construct consists of the assembly of all CUE and flanking sequences at their original location except that BgII-BamHII linker sequences separate each element.

35 Fig. 12 represents the plasmid maps.

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Fig. 13 shows the effect of re-transfecting primary transfectants on GFP expression. Cells (CHO-DG44) were co-transfected with pSV40EGFP (left tube) or pMAR-SV40EGFP (central tube) and pSVneo as resistance plasmid. Cells transfected with pMAR-SV40EGFP were re-transfected 24 hours later with the same plasmid and a different selection plasmid, pSVpuro (right tube). After two weeks selection, the phenotype of the stably transfected cell population was analysed by FACS.

Fig. 14 shows the effect of multiple load of MAR-containing plasmid. The pMAR-SV40EGFP/pMAR-SV40EGFP secondary transfectants were used in a third cycle of transfection at the end of the selection process. The tertiary transfection was accomplished with pMAR or pMAR-SV40EGFP to give tertiary transfectants. After 24 hours, cells were transfected again with either plasmid, resulting in the quaternary transfectants (see Table 4).

Fig. 15 shows comparative performance of SMAR prediction algorithms exemplified by region WP18A10A7. (A) SMAR Scan® analysis was performed with default settings. (B) SIDD analysis (top curve and left-hand side scale), and the attachment of several

DNA fragments to the nuclear matrix in vitro (bar-graph, right-hand side scale) was taken from Goetze et al (Goetze S, Gluch A, Benham C, Bode J, "Computational and in vitro analysis of destabilized DNA regions in the interferon gene cluster: potential of predicting functional gene domains." *Biochemistry*, 42:154-166, 2003).

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Fig. 16 represents the results of a a gene therapy-like protocol using MARs. The group of mice injected by MAR-network, induced from the beginning of the experiment, display a better induction of the hematocrit in comparison of mice injected by original network without MAR. After 2 months, hematocrits in "MAR-containing group" is still at values higher (65%) than normal hematocrit levels (45-55%).

Fig. 17 represents the scatterplot for the 1757 S/MAR sequences of the AT (top) and TA (bottom) dinucleotide percentages versus the predicted DNA bending as computed by SMAR Scan®.

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Fig. 18 represents the dinucleotide percentage distribution plots over the 1757 non-S/MARs sequences.

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Fig. 19 shows the effect of various S/MAR elements on the production of recombinant green fluorescent protein (GFP). Populations of CHO cells transfected with a GFP expression vector containing or a MAR element, as indicated, were analyzed by a fluorescence-activated cell sorter (FACS®), and typical profiles are shown. The profiles display the cell number counts as a function of the GFP fluorescence levels.

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Fig. 20 depicts the effect of the induction of hematocrit in mice injected by MAR-network.

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### **DETAILED DESCRIPTION OF THE INVENTION**

The present invention relates to a purified and isolated DNA sequence having protein production increasing activity characterized in that said DNA sequence comprises at least one bent DNA element, and at least one binding site for a DNA binding protein.

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Certain sequences of DNA are known to form a relatively "static curve", where the DNA follows a particular 3-dimensional path. Thus, instead of just being in the normal B-DNA conformation ("straight"), the piece of DNA can form a flat, planar curve also defined as bent DNA (Marini, et al., 1982 "Bent helical structure in kinetoplast DNA", *Proc. Natl. Acad. Sci. USA*, 79: 7664-7664).

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Surprisingly, Applicants have shown that the bent DNA element of a purified and isolated DNA sequence having protein production increasing activity of the present invention usually contains at least 10% of dinucleotide TA, and/or at least 12% of dinucleotide AT on a stretch of 100 contiguous base pairs. Preferably, the bent DNA element contains at least 33% of dinucleotide TA, and/or at least 33% of dinucleotide AT on a stretch of 100 contiguous base pairs. These data have been obtained by the method described further.

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According to the present invention, the purified and isolated DNA sequence usually comprises a MAR nucleotide sequence selected from the group comprising the sequences SEQ ID Nos 1 to 27 or a cLysMAR element or a fragment thereof. Preferably, the purified and isolated DNA sequence is a MAR nucleotide sequence

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WO 2005/040377 PCT/EP2004/011974 selected from the group comprising the sequences SEQ ID Nos 1 to 27, more preferably the sequences SEQ ID Nos 24 to 27.

Encompassed by the present invention are as well complementary sequences of the above-mentioned sequences SEQ ID Nos 1 to 27 and the cLysMAR element or fragment, which can be produced by using PCR or other means.

An "element" is a conserved nucleotide sequences that bears common functional properties (i.e. binding sites for transcription factors) or structural (i.e. bent DNA sequence) features.

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A part of sequences SEQ ID Nos 1 to 27 and the cLysMAR element or fragment refers to sequences sharing at least 70% nucleotides in length with the respective sequence of the SEQ ID Nos 1 to 27. These sequences can be used as long as they exhibit the same properties as the native sequence from which they derive. Preferably these sequences share more than 80%, in particular more than 90% nucleotides in length with the respective sequence of the SEQ ID Nos 1 to 27.

The present invention also includes variants of the aforementioned sequences SEQ ID Nos 1 to 27 and the cLysMAR element or fragment, that is nucleotide sequences that vary from the reference sequence by conservative nucleotide substitutions, whereby one or more nucleotides are substituted by another with same characteristics.

The sequences SEQ ID Nos 1 to 23 have been identified by scanning human chromosome 1 and 2 using SMAR Scan®, showing that the identification of novel MAR sequences is feasible using the tools reported thereafter whereas SEQ ID No 24 to 27 have been identified by scanning the complete human genome using the combined SMAR Scan® method.

In a first step, the complete chromosome 1 and 2 were screened to identify bent DNA element as region corresponding to the highest bent, major groove depth, minor groove width and lowest melting temperature as shown in figure 3. In a second step, this collection of sequence was scanned for binding sites of regulatory proteins such as SATB1, GATA, etc. as shown in the figure 8B) yielding sequences SEQ ID 1-23.

Furthermore, sequences 21-23 were further shown to be located next to known gene from the Human Genome Data Base.

With regard to SEQ ID No 24 to 27 these sequences have been yielded by scanning the human genome according to the combined method and were selected as examples among 1757 MAR elements so detected.

Molecular chimera of MAR sequences are also considered in the present invention. By molecular chimera is intended a nucleotide sequence that may include a functional portion of a MAR element and that will be obtained by molecular biology methods known by those skilled in the art.

Particular combinations of MAR elements or fragments or sub-portions thereof are also considered in the present invention. These fragments can be prepared by a variety of methods known in the art. These methods include, but are not limited to, digestion with restriction enzymes and recovery of the fragments, chemical synthesis or polymerase chain reactions (PCR).

Therefore, particular combinations of elements or fragments of the sequences SEQ ID

Nos 1 to 27 and cLysMAR elements or fragments are also envisioned in the present invention, depending on the functional results to be obtained. Elements of the cLysMAR are e.g. the B, K and F regions as described in WO 02/074969, the disclosure of which is hereby incorporated herein by reference, in its entirety. The preferred elements of the cLysMAR used in the present invention are the B, K and F regions. Only one element might be used or multiple copies of the same or distinct elements (multimerized elements) might be used (see Fig. 8 A)).

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By fragment is intended a portion of the respective nucleotide sequence. Fragments of a MAR nucleotide sequence may retain biological activity and hence bind to purified nuclear matrices and/or alter the expression patterns of coding sequences operably linked to a promoter. Fragments of a MAR nucleotide sequence may range from at least about 100 to 1000 bp, preferably from about 200 to 700 bp, more preferably from about 300 to 500 bp nucleotides. Also envisioned are any combinations of fragments, which have the same number of nucleotides present in a synthetic MAR sequence consisting of natural MAR element and/or fragments. The fragments are preferably assembled by linker sequences. Preferred linkers are BgIII-BamHI linker.

"Protein production increasing activity" refers to an activity of the purified and isolated

DNA sequence defined as follows: after having been introduced under suitable conditions into a eukaryotic host cell, the sequence is capable of increasing protein production levels in cell culture as compared to a culture of cell transfected without said DNA sequence. Usually the increase is 1.5 to 10 fold, preferably 4 to 10 fold. This corresponds to a production rate or a specific cellular productivity of at least 10 pg per cell per day (see Example 11 and Fig.13).

As used herein, the following definitions are supplied in order to facilitate the understanding of this invention.

30 "Chromatin" is the protein and nucleic acid material constituting the chromosomes of a eukaryotic cell, and refers to DNA, RNA and associated proteins.

A "chromatin element" means a nucleic acid sequence on a chromosome having the property to modify the chromatine structure when integrated into that chromosome.

"Cis" refers to the placement of two or more elements (such as chromatin elements) on the same nucleic acid molecule (such as the same vector, plasmid or chromosome).

"Trans" refers to the placement of two or more elements (such as chromatin elements) on two or more different nucleic acid molecules (such as on two vectors or two chromosomes).

Chromatin modifying elements that are potentially capable of overcoming position effects, and hence are of interest for the development of stable cell lines, include boundary elements (BEs), matrix attachment regions (MARs), locus control regions (LCRs), and universal chromatin opening elements (UCOEs).

Boundary elements ("BEs"), or insulator elements, define boundaries in chromatin in many cases (Bell A and Felsenfeld G. 1999; "Stopped at the border: boundaries and insulators, *Curr Opin Genet Dev* 9, 191-198) and may play a role in defining a transcriptional domain in vivo. BEs lack intrinsic promoter/enhancer activity, but rather are thought to protect genes from the transcriptional influence of regulatory elements in the surrounding chromatin. The enhancer-block assay is commonly used to identify

insulator elements. In this assay, the chromatin element is placed between an enhancer and a promoter, and enhancer-activated transcription is measured. Boundary elements have been shown to be able to protect stably transfected reporter genes against position effects in Drosophila, yeast and in mammalian cells. They have also been shown to increase the proportion of transgenic mice with inducible transgene expression.

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Locus control regions ("LCRs") are cis-regulatory elements required for the initial chromatin activation of a locus and subsequent gene transcription in their native locations (Grosveld, F. 1999, "Activation by locus control regions?" *Curr Opin Genet Dev* 9, 152-157). The activating function of LCRs also allows the expression of a coupled transgene in the appropriate tissue in transgenic mice, irrespective of the site of integration in the host genome. While LCRs generally confer tissue-specific levels of expression on linked genes, efficient expression in nearly all tissues in transgenic mice has been reported for a truncated human T-cell receptor LCR and a rat LAP LCR. The most extensively characterized LCR is that of the globin locus. Its use in vectors for the gene therapy of sickle cell disease and (3-thalassemias is currently being evaluated.

"MARs". according to a well-accepted model, may mediate the anchorage of specific 20 DNA sequence to the nuclear matrix, generating chromatin loop domains that extend outwards from the heterochromatin cores. While MARs do not contain any obvious consensus or recognizable sequence, their most consistent feature appears to be an overall high A/T content, and C bases predominating on one strand (Bode J, Schlake T, RiosRamirez M. Mielke C, Stengart M, Kay V and KlehrWirth D, "Scaffold/matrix-25 attached regions: structural propreties creating transcriptionally active loci", Structural and Functional Organization of the Nuclear Matrix: International Review of Citology, 162A:389453, 1995). These regions have a propensity to form bent secondary structures that may be prone to strand separation. They are often referred to as baseunpairing regions (BURs), and they contain a core-unwinding element (CUE) that might represent the nucleation point of strand separation (Benham C and al., Stress induced 30 duplex DNA destabilization in scaffold/matrix attachment regions, J. Mol. Biol., 274:181-196, 1997). Several simple AT-rich sequence motifs have often been found within MAR sequences, but for the most part, their functional importance and potential mode of action remain unclear. These include the A-box (AATAAAYAAA), the T-box (TTWTWTTWTT), DNA unwinding motifs (AATATATT, AATATT), SATB1 binding sites 35 (H-box, A/T/C25) and consensus Topoisomerase II sites for vertebrates

Ubiquitous chromatin opening elements ("UCOEs", also known as "ubiquitously-acting chromatin opening elements") have been reported in WO 00/05393.

(RNYNNCNNGYNGKTNYNY) or Drosophila (GTNWAYATTNATNNR).

An "enhancer" is a nucleotide sequence that acts to potentiate the transcription of genes independent of the identity of the gene, the position of the sequence in relation to the gene, or the orientation of the sequence. The vectors of the present invention optionally include enhancers.

A "gene" is a deoxyribonucleotide (DNA) sequence coding for a given mature protein. As used herein, the term "gene" shall not include untranslated flanking regions such as RNA transcription initiation signals, polyadenylation addition sites, promoters or enhancers.

A "product gene" is a gene that encodes a protein product having desirable characteristics such as diagnostic or therapeutic utility. A product gene includes, e. g.,

structural genes and regulatory genes.

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A "structural gene" refers to a gene that encodes a structural protein. Examples of structural genes include but are not limited to, cytoskeletal proteins, extracellular matrix proteins, enzymes, nuclear pore proteins and nuclear scaffold proteins, ion channels and transporters, contractile proteins, and chaperones. Preferred structural genes encode for antibodies or antibody fragments.

A "regulatory gene" refers to a gene that encodes a regulatory protein. Examples of regulatory proteins include, but are not limited to, transcription factors, hormones, growth factors, cytokines, signal transduction molecules, oncogenes, proto-oncogenes, transmembrane receptors, and protein kinases.

"Orientation" refers to the order of nucleotides in a given DNA sequence. For example, an inverted orientation of a DNA sequence is one in which the 5' to 3' order of the sequence in relation to another sequence is reversed when compared to a point of reference in the DNA from which the sequence was obtained. Such reference points can include the direction of transcription of other specified DNA sequences in the source DNA and/or the origin of replication of replicable vectors containing the sequence.

"Eukaryotic cell" refers to any mammalian or non-mammalian cell from a eukaryotic organism. By way of non-limiting example, any eukaryotic cell that is capable of being maintained under cell culture conditions and subsequently transfected would be included in this invention. Especially preferable cell types include, e. g., stem cells, embryonic stem cells, Chinese hamster ovary cells (CHO), COS, BHK21, NIH3T3, HeLa, C2C12, cancer cells, and primary differentiated or undifferentiated cells. Other suitable host cells are known to those skilled in the art.

The terms "host cell" and "recombinant host cell" are used interchangeably herein to indicate a eukaryotic cell into which one or more vectors of the invention have been introduced. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The terms "introducing a purified DNA into a eukaryotic host cell" or "transfection" denote any process wherein an extracellular DNA, with or without accompanying material, enters a host cell. The term "cell transfected" or "transfected cell" means the cell into which the extracellular DNA has been introduced and thus harbours the extracellular DNA. The DNA might be introduced into the cell so that the nucleic acid is replicable either as a chromosomal integrant or as an extra chromosomal element.

"Promoter" as used herein refers to a nucleic acid sequence that regulates expression of a gene.

"Co-transfection" means the process of transfecting a eukaryotic cell with more than one exogenous gene, or vector, or plasmid, foreign to the cell, one of which may confer a selectable phenotype on the cell.

The purified and isolated DNA sequence having protein production increasing activity also comprises, besides one or more bent DNA element, at least one binding site for a DNA binding protein.

Usually the DNA binding protein is a transcription factor. Examples of transcription factors are the group comprising the polyQpolyP domain proteins.

Another example of a transcription factor is a transcription factor selected from the group comprising SATB1, NMP4, MEF2, S8, DLX1, FREAC7, BRN2, GATA 1/3, TATA, Bright, MSX, AP1, C/EBP, CREBP1, FOX, Freac7, HFH1, HNF3alpha, Nkx25,

10 POU3F2, Pit1, TTF1, XFD1, AR, C/EBPgamma, Cdc5, FOXD3, HFH3, HNF3 beta, MRF2, Oct1, POU6F1, SRF, V\$MTATA\_B, XFD2, Bach2, CDP CR3, Cdx2, FOXJ2, HFL, HP1, Myc, PBX, Pax3, TEF, VBP, XFD3, Brn2, COMP1, Evil, FOXP3, GATA4, HFN1, Lhx3, NKX3A, POU1F1, Pax6, TFIIA or a combination of two or more of these transcription factors are preferred. Most preferred are SATB1, NMP4, MEF2 and polyQpolyP domain proteins.

SATB1, NMP4 and MEF2, for example, are known to regulate the development and/or tissue-specific gene expression in mammals. These transcription factors have the capacity to alter DNA geometry, and reciprocally, binding to DNA as an allosteric ligand modifies their structure. Recently, SATB1 was found to form a cage-like structure circumscribing heterochromatin (Cai S, Han HJ, and Kohwi-Shigematsu T, "Tissue-specific nuclear architecture and gene expression regulated by SATB1" *Nat Genet*, 2003. 34(1): p. 42-51).

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- Yet another object of the present invention is to provide a purified and isolated cLysMAR element and/or fragment, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- 30 More preferably, the cLysMAR element and/or fragment are consisting of at least one nucleotide sequence selected from the B, K and F regions.

A further object of the present invention is to provide a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences.

Preferably, the synthetic MAR sequence comprises a cLysMAR element and/or fragment a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants. Also preferably, linker sequences are BgIII-BamHI linker.

An other aspect of the invention is to provide a method for identifying a MAR sequence using a Bioinformatic tool comprising the computing of values of one or more DNA sequence features corresponding to DNA bending, major groove depth and minor groove width potentials and melting temperature. Preferably, the identification of one or more DNA sequence features further comprises a further DNA sequence feature corresponding to binding sites for DNA binding proteins, which is also computed with this method.

50 Preferably, profiles or weight-matrices of said bioinformatic tool are based on dinucleotide recognition.

The bioinformatic tool used for the present method is preferably, SMAR Scan®, which contains algorithms developed by Gene Express (<a href="http://srs6.bionet.nsc.ru/srs6bin/cgibin/wgetz">http://srs6.bionet.nsc.ru/srs6bin/cgibin/wgetz</a>?-e+[FEATURES-SiteID:'nR']) and based on Levitsky *et al.*, 1999. These algorithms recognise profiles, based on dinucleotides weight-matrices, to compute the theoretical values for conformational and physicochemical properties of DNA.

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Preferably, SMAR Scan® uses the four theoretical criteria also designated as DNA sequence features corresponding to DNA bending, major groove depth and minor groove width potentials, melting temperature in all possible combination, using scanning windows of variable size (see Fig. 3). For each function used, a cut-off value has to be set. The program returns a hit every time the computed score of a given region is above the set cut-off value for all of the chosen criteria. Two data output modes are available to handle the hits, the first (called "profile-like") simply returns all hit positions on the query sequence and their corresponding values for the different criteria chosen. The second mode (called "contiguous hits") returns only the positions of several contiguous hits and their corresponding sequence. For this mode, the minimum number of contiguous hits is another cut-off value that can be set, again with a tunable window size. This second mode is the default mode of SMAR Scan®. Indeed, from a semantic point of view, a hit is considered as a core-unwinding element (CUE), and a cluster of CUEs accompanied by clusters of binding sites for relevant proteins is considered as a MAR. Thus, SMAR Scan® considers only several contiguous hits as a potential MAR.

To tune the default cut-off values for the four theoretical structural criteria, experimentally validated MARs from SMARt DB (http://transfac.gbf.de/- SMARt DB) were used. All the human MAR sequences from the database were retrieved and analyzed with SMAR Scan® using the "profile-like" mode with the four criteria and with no set cut-off value. This allowed the setting of each function for every position of the sequences. The distribution for each criterion was then computed according to these data (see Fig. 1 and 3).

The default cut-off values of SMAR Scan® for the bend, the major groove depth and the minor groove width were set at the average of the 75th quantile and the median. For the melting temperature, the default cut-off value should be set at the 75th quantile. The minimum length for the "contiguous-hits" mode should be set to 300 because it is assumed to be the minimum length of a MAR (see Fig. 8 and 9). However, one skilled in the art would be able to determine the cut-off values for the above-mentioned criteria for a given organism with minimal experimentation.

40 Preferably, DNA bending values are comprised between 3 to 5 ° (radial degree). Most preferably they are situated between 3.8 to 4.4 °, corresponding to the smallest peak of Fig. 1.

Preferably the major groove depth values are comprised between 8.9 to 9.3 Å

(Angström) and minor groove width values between 5.2 to 5.8 Å. Most preferably the major groove depth values are comprised between 9.0 to 9.2 Å and minor groove width values between 5.4 to 5.7 Å.

Preferably the melting temperature is comprised between 55 to 75 ° C (Celsius degree). Most preferably, the melting temperature is comprised between 55 to 62 ° C.

The DNA binding protein of which values can be computed by the method is usually a transcription factor preferably a polyQpolyP domain or a transcription factor selected

from the group comprising SATB1, NMP4, MEF2, S8, DLX1, FREAC7, BRN2, GATA 1/3, TATA, Bright, MSX, AP1, C/EBP, CREBP1, FOX, Freac7, HFH1, HNF3alpha, Nkx25, POU3F2, Pit1, TTF1, XFD1, AR, C/EBPgamma, Cdc5, FOXD3, HFH3, HNF3 beta, MRF2, Oct1, POU6F1, SRF, V\$MTATA\_B, XFD2, Bach2, CDP CR3, Cdx2, FOXJ2, HFL, HP1, Myc, PBX, Pax3, TEF, VBP, XFD3, Brn2, COMP1, Evil, FOXP3, GATA4, HFN1, Lhx3, NKX3A, POU1F1, Pax6, TFIIA or a combination of two or more of these transcription factors.

However, one skilled in the art would be able to determine other kinds of transcription factors in order to carry out the method according to the present invention.

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In case SMAR Scan® is envisaged to perform, for example, large scale analysis, then, preferably, the above-mentioned method further comprises at least one filter predicting DNA binding sites for DNA transcription factors in order to reduce the computation.

The principle of this method combines SMAR Scan® to compute the structural features as described above and a filter, such as for example, the pfsearch, (from the pftools package as described in Bucher P, Karplus K, Moeri N, and Hofmann K, "A flexible search technique based on generalized profiles", *Computers and Chemistry*, 20:324, 1996) to predict the binding of some transcription factors.

Examples of filters comprise, but are not limited to, pfsearch, MatInspector, RMatch Professional and TRANSFAC Professional

This combined method uses the structural features of SMAR Scan® and the predicted binding of specific transcription factors of the filter that can be applied sequentially in any order to select MARs, therefore, depending on the filter is applied at the beginning or at the end of the method.

The first level selects sequences out of the primary input sequence and the second level, consisting in the filter, may be used to restrain among the selected sequences those which satisfy the criteria used by the filter.

In this combined method the filter detects clusters of DNA binding sites using profiles or weightmatrices from, for example, MatInspector (Quandt K, Frech K, Karas H, Wingender E, Werner T, "MatInd and MatInspector New fast and versatile tools for detection of consensus matches in nucleotide sequence data", *Nucleic Acids Research*, 23, 48784884, 1995.). The filter can also detect densities of clusters of DNA binding sites.

The combined method is actually a "wrapper" written in Perl for SMAR Scan® and, in case the pfsearch is used as a filter, from the pftools. The combined method performs a twolevel processing using at each level one of these tools (SMAR Scan® or filter) as a potential "filter", each filter being optional and possible to be used to compute the predicted features without doing any filtering.

If SMAR Scan® is used in the first level to filter subsequences, it has to be used with the "all the contiguous hits" mode in order to return sequences. If the pfsearch is used in the first level as first filter, it has to be used with only one profile and a distance in nucleotide needs to be provided. This distance is used to group together pfsearch hits that are located at a distance inferior to the distance provided in order to return sequences; The combined method launches pfsearch, parses its output and returns

sequences corresponding to pfsearch hits that are grouped together according to the distance provided. Then whatever the tool used in the first level, the length of the subsequences thus selected can be systematically extended at both ends according to a parameter called "hits extension".

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The second and optional level can be used to filter out sequences (already filtered sequences or unfiltered input sequences) or to get the results of SMAR Scan® and/or pfsearch without doing any filtering on these sequences. If the second level of combined method is used to filter, for each criteria considered cutoff values (hit per nucleotide) need to be provided to filter out those sequences (see Fig. 20).

Another concern of the present invention is also to provide a method for identifying a MAR sequence comprising at least one filter detecting clusters of DNA binding sites using profiles or weightmatrices. Preferably, this method comprises two levels of filters and in this case, SMAR Scan® is totally absent from said method. Usually, the two levels consist in pfsearch.

Also embraced by the present invention is a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter.

Analysis by the combined method of the whole human genome yielded a total of 1757 putative MARs representing a total of 1 065 305 base paires. In order to reduce the number of results, a dinucleotide analysis was performed on these 1757 MARs, computing each of the 16 possible dinucleotide percentage for each sequence considering both strands in the 5' to 3' direction.

Surprisingly, Applicants have shown that all of the "super" MARs detected with the combined method contain at least 10% of dinucleotide TA on a stretch of 100 contiguous base pairs. Preferably, these sequences contain at least 33% of dinucleotide TA on a stretch of 100 contiguous base pairs.

Applicants have also shown that these same sequences further contain at least 12% of dinucleotide AT on a stretch of 100 contiguous base pairs. Preferably, they contain at least 33% of dinucleotide AT on a stretch of 100 contiguous base pairs.

An other aspect of the invention is to provide a purified and isolated MAR DNA sequence of any of the preceding described MARs, comprising a sequence selected from the sequences SEQ ID Nos 1 to 27, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.

Preferably, said purified and isolated MAR DNA sequence comprises a sequence selected from the sequences SEQ ID Nos 24 to 27, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants. These sequences 24 to 27 correspond to those detected by the combined method and show a higher protein production increasing activity over sequences 1 to 23.

The present invention also encompasses the use of a purified and isolated DNA sequence comprising a first isolated matrix attachment region (MAR) nucleotide sequence which is a MAR nucleotide sequence selected from the group comprising

 a purified and isolated DNA sequence having protein production increasing activity,

- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter,
- the sequences SEQ ID Nos 1 to 27,

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- a purified and isolated cLysMAR element and/or fragment,
- a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences,
- a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants or a MAR nucleotide sequence of a cLysMAR element and/or fragment, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants for increasing protein production activity in a eukaryotic host cell.

Said purified and isolated DNA sequence usually further comprises one or more regulatory sequences, as known in the art e.g. a promoter and/or an enhancer, polyadenylation sites and splice junctions usually employed for the expression of the protein or may optionally encode a selectable marker. Preferably said purified and isolated DNA sequence comprises a promoter which is operably linked to a gene of interest.

The DNA sequences of this invention can be isolated according to standard PCR protocols and methods well known in the art.

Promoters which can be used provided that such promoters are compatible with the host cell are, for example, promoters obtained from the genomes of viruses such as polyoma virus, adenovirus (such as Adenovirus 2), papilloma virus (such as bovine papilloma virus), avian sarcoma virus, cytomegalovirus (such as murine or human cytomegalovirus immediate early promoter), a retrovirus, hepatitis-B virus, and Simian Virus 40 (such as SV 40 early and late promoters) or promoters obtained from heterologous mammalian promoters, such as the actin promoter or an immunoglobulin promoter or heat shock promoters. Such regulatory sequences direct constitutive expression.

Furthermore, the purified and isolated DNA sequence might further comprise regulatory sequences which are capable of directing expression of the nucleic acid preferentially in a particular cell type (e. g., tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, et al., 1987. Genes Dev.1: 268-277), lymphoid-specific promoters (Calame and Eaton, 1988. Adv. Immunol. 43: 235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989. EMBOJ. 8: 729-733) and immunoglobulins (Banerji, etal., 1983. Cell 33: 729-740; Queen and Baltimore, 1983. Cell 33:741-748), neuron-specific promoters (e. g., the neurofilament promoter; Byrne and Ruddle, 1989. Proc.Natl. Acad. Sci. USA 86: 5473-5477), pancreas-specific promoters (Edlund, et al., 1985. Science 230: 912-916), and mammary gland-specific promoters (e. g., milk whey promoter; U. S. Pat. No. 4,873,316 and European Application No. 264,166).

Developmentally-regulated promoters are also encompassed. Examples of such promoters include, e.g., the murine hox promoters (Kessel and Gruss, 1990. Science 249: 374-379) and thea-fetoprotein promoter (Campes and Tilghman, 1989. Genes

Dev. 3: 537-546).

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Regulatable gene expression promoters are well known in the art, and include, by way of non-limiting example, any promoter that modulates expression of a gene encoding a desired protein by binding an exogenous molecule, such as the CRE/LOX system, the TET system, the doxycycline system, the NFkappaB/UV light system, the Leu3p/isopropylmalate system, and theGLVPc/GAL4 system (See e. g., Sauer, 1998, Methods 14 (4): 381-92; Lewandoski, 2001, Nat. Rev. Genet 2 (10): 743-55; Legrand-Poels et al., 1998, J. Photochem. Photobiol. B. 45: 18; Guo et al., 1996, FEBS Lett. 390 (2): 191-5; Wang et al., PNAS USA, 1999,96 (15): 84838). However, one skilled in the art would be able to determine other kinds of promoters that are suitable in carrying out the present invention.

Enhancers can be optionally included in the purified DNA sequence of the invention then belonging to the regulatory sequence, e.g. the promoter.

The "gene of interest" or "transgene" preferably encodes a protein (structural or regulatory protein). As used herein "protein" refers generally to peptides and polypeptides having more than about ten amino acids. The proteins may be "homologous" to the host (i.e., endogenous to the host cell being utilized), or "heterologous." (i.e., foreign to the host cell being utilized), such as a human protein produced by yeast. The protein may be produced as an insoluble aggregate or as a soluble protein in the periplasmic space or cytoplasm of the cell, or in the extracellular medium. Examples of proteins include hormones such as growth hormone or erythropoietin (EPO), growth factors such as epidermal growth factor, analgesic substances like enkephalin, enzymes like chymotrypsin, receptors to hormones or growth factors, antibodies and include as well proteins usually used as a visualizing marker e.g. green fluorescent protein.

Preferably the purified DNA sequence further comprises at least a second isolated 30 matrix attachment region (MAR) nucleotide sequence selected from the group comprising

- a purified and isolated DNA sequence having protein production increasing
- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter,
- the sequences SEQ ID Nos 1 to 27.
- a purified and isolated cLysMAR element and/or fragment,
- a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences,

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants. The isolated matrix attachment region (MAR) nucleotide sequence might be identical or different. Alternatively, a first and a second identical MAR nucleotide sequence are used.

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Preferably, the MAR nucleotide sequences are located at both the 5' and the 3' ends of the sequence containing the promoter and the gene of interest. But the invention also envisions the fact that said first and or at least second MAR nucleotide sequences are located on a sequence distinct from the one containing the promoter and the gene of interest.

Embraced by the scope of the present invention is also the purified and isolated DNA sequence comprising a first isolated matrix attachment region (MAR) nucleotide sequence which is a MAR nucleotide sequence selected from the group comprising

- a purified and isolated DNA sequence having protein production increasing activity,

- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter,

- the sequences SEQ ID Nos 1 to 27,

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- a purified and isolated cLysMAR element and/or fragment,

- a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences,

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants that can be used for increasing protein production activity in a eukaryotic host cell by introducing the purified and isolated DNA sequence into a eukaryotic host cell according to well known protocols. Usually applied methods for introducing DNA into eukaryotic host cells applied are e.g. direct introduction of cloned DNA by microinjection or microparticle bombardment; electrotransfer ;use of viral vectors; encapsulation within a carrier system; and use of transfecting reagents such as calcium phosphate, diethylaminoethyl (DEAE) –dextran or commercial transfection systems like the Lipofect-AMINE 2000 (Invitrogen). Preferably, the transfection method used to introduce the purified DNA sequence into a eukaryotic host cell is the method for transfecting a eukaryotic cell as described below.

The purified and isolated DNA sequence can be used in the form of a circular vector. Preferably, the purified and isolated DNA sequence is used in the form of a linear DNA sequence as vector.

As used herein, "plasmid" and "vector" are used interchangeably, as the plasmid is the most commonly used vector form. However, the invention is intended to include such other forms of expression vectors, including, but not limited to, viral vectors (e. g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The present invention further encompasses a method for transfecting a eukaryotic host cell, said method comprising

- a) introducing into said eukaryotic host cell at least one purified DNA sequence comprising at least one DNA sequence of interest and/or at least one purified and isolated DNA sequence comprising a MAR nucleotide sequence or other chromatin modifying elements,
- b) subjecting within a defined time said transfected eukaryotic host cell to at least one additional transfection step with at least one purified DNA sequence comprising at least one DNA sequence of interest and/or with at least one purified and isolated DNA sequence comprising a MAR nucleotide sequence or other chromatin modifying elements
- c) selecting said transfected eukaryotic host cell.

Preferably at least two up to four transfecting steps are applied in step b).

In order to select the successful transfected cells, a gene that encodes a selectable marker (e. g., resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. The gene that encodes a selectable marker might be located

on the purified DNA sequence comprising at least one DNA sequence of interest and/or at least one purified and isolated DNA sequence consisting of a MAR nucleotide sequence or other chromatin modifying elements or might optionally be co-introduced in separate form e.g. on a plasmid. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. The amount of the drug can be adapted as desired in order to increase productivity

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Usually, one or more selectable markers are used. Preferably, the selectable markers used in each distinct transfection steps are different. This allows selecting the transformed cells that are "multi-transformed" by using for example two different antibiotic selections.

Any eukaryotic host cell capable of protein production and lacking a cell wall can be used in the methods of the invention. Examples of useful mammalian host cell lines include human cells such as human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol 36, 59 (1977)), human cervical carcinoma cells (HELA, ATCC CCL 2), human lung cells (W138, ATCC CCL 75), human liver cells (Hep G2, HB 8065); rodent cells such as baby hamster kidney cells (BHK, ATCC CCL 10), Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, *Proc. Natl. Acad. Sci. USA*, 77, 4216 (1980)), mouse sertoli cells (TM4, Mather, *Biol. Reprod* 23, 243-251 (1980)), mouse mammary tumor (MMT 060562, ATCC CCL51); and cells from other mammals such as monkey kidney CV1 line transformed by SV4O (COS-7, ATCC CRL 1651); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); myeloma (e.g. NS0)

ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); myeloma (e.g. NS0)
/hybridoma cells.

Preferably, the selected transfected eukaryotic host cells are high protein producer cells with a production rate of at least 10 pg per cell per day.

Most preferred for uses herein are mammalian cells, more preferred are CHO cells.

The DNA sequence of interest of the purified and isolated DNA sequence is usually a gene of interest preferably encoding a protein operably linked to a promoter as described above. The purified and isolated DNA sequence comprising at least one DNA sequence of interest might comprise additionally to the DNA sequence of interest MAR nucleotide sequence or other chromatin modifying elements.

Purified and isolated DNA sequence comprising a MAR nucleotide sequence are for example selected from the group comprising the sequences SEQ ID Nos 1 to 27 and/or particular elements of the cLysMAR e.g. the B, K and F regions as well as fragment and elements and combinations thereof as described above. Other chromatin modifying elements are for example boundary elements (BEs), locus control regions (LCRs), and universal chromatin opening elements (UCOEs) (see Zahn-Zabal et al. already cited). An example of multiple transfections of host cells is shown in Example 12 (Table 3). The first transfecting step (primary transfection) is carried out with the gene of interest (SV40EGFP) alone, with a MAR nucleotide sequence (MAR-SV40EGFP). The second transfecting step (secondary transfection) is carried out with the gene of interest (SV40EGFP) alone, with a MAR nucleotide sequence (MAR) alone or with the gene of interest and a MAR nucleotide sequence (MAR) alone or with the gene of interest and a MAR nucleotide sequence (MAR-SV40EGFP), in all possible combinations resulting from the first transfecting step.

Preferably the eukaryotic host cell is transfected by:

a) introducing a purified DNA sequence comprising one DNA sequence of interest and additionally a MAR nucleotide sequence,

b) subjecting within a defined time said transfected eukaryotic host cell to at least one additional transfection step with the same purified DNA sequence comprising one DNA sequence of interest and additionally a MAR nucleotide sequence of step a).

Also preferably, the MAR nucleotide sequence of the of the purified and isolated DNA sequence is selected form the group comprising

a purified and isolated DNA sequence having protein production increasing activity,

- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter,
- the sequences SEQ ID Nos 1 to 27,

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- a purified and isolated cLysMAR element and/or fragment,

- a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences,

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.

Surprisingly, a synergy between the first and second transfection has been observed. A particular synergy has been observed when MAR elements are present at one or both of the transfection steps. Multiple transfections of the cells with pMAR alone or in combination with various expression plasmids, using the method described above have been carried out. For example, Table 3 shows that transfecting the cells twice with the pMAR-SV40EGFP plasmid gave the highest expression of GFP and the highest degree of enhancement of all conditions (4.3 fold). In contrast, transfecting twice the vector without MAR gave little or no enhancement, 2.8-fold, instead of the expected two-fold increase. This proves that the presence of MAR elements at each transfection step is of particular interest to achieve the maximal protein synthesis.

As a particular example of the transfection method, said purified DNA sequence comprising at least one DNA sequence of interest can be introduced in form of multiple unlinked plasmids, comprising a gene of interest operably linked to a promoter, a selectable marker gene, and/or protein production increasing elements such as MAR sequences.

The ratio of the first and subsequent DNA sequences may be adapted as required for the use of specific cell types, and is routine experimentation to one ordinary skilled in the art.

The defined time for additional transformations of the primary transformed cells is tightly dependent on the cell cycle and on its duration. Usually the defined time corresponds to intervals related to the cell division cycle.

Therefore this precise timing may be adapted as required for the use of specific cell types, and is routine experimentation to one ordinary skilled in the art.

Preferably the defined time is the moment the host cell just has entered into the same phase of a second or a further cell division cycle, preferably the second cycle.

This time is usually situated between 6h and 48 h, preferably between 20h and 24h after the previous transfecting event.

Also encompassed by the present invention is a method for transfecting a eukaryotic host cell, said method comprising co-transfecting into said eukaryotic host cell at least one first purified and isolated DNA sequence comprising at least one DNA sequence of

interest, and a second purified DNA comprising at least one MAR nucleotide selected from the group comprising:

- a purified and isolated DNA sequence having protein production increasing activity,

- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter,
- the sequences SEQ ID Nos 1 to 27,

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- a purified and isolated cLysMAR element and/or fragment,

- a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences,

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants. Said first purified and isolated DNA sequence can also comprise at least one MAR nucleotide as described above.

Also envisioned is a process for the production of a protein wherein a eukaryotic host cell is transfected according to the transfection methods as defined in the present invention and is cultured in a culture medium under conditions suitable for expression of the protein. Said protein is finally recovered according to any recovering process known to the skilled in the art.

Given as an example, the following process for protein production might be used. The eukaryotic host cell transfected with the transfection method of the present invention is used in a process for the production of a protein by culturing said cell under conditions suitable for expression of said protein and recovering said protein. Suitable culture conditions are those conventionally used for in vitro cultivation of eukaryotic cells as described e.g. in WO 96/39488. The protein can be isolated from the cell culture by conventional separation techniques such as e.g. fractionation on immunoaffinity or ion-exchange columns; precipitation; reverse phase HPLC; chromatography; chromatofocusing; SDS-PAGE; gel filtration. One skilled in the art will appreciate that purification methods suitable for the polypeptide of interest may require modification to account for changes in the character of the polypeptide upon expression in recombinant cell culture.

The proteins that are produced according to this invention can be tested for functionality by a variety of methods. For example, the presence of antigenic epitopes and ability of the proteins to bind ligands can be determined by Western blot assays, fluorescence cell sorting assays, immunoprecipitation, immunochemical assays and/or competitive binding assays, as well as any other assay which measures specific binding activity.

The proteins of this invention can be used in a number of practical applications including, but not limited to:

- 1. Immunization with recombinant host protein antigen as a viral/pathogen antagonist.
- 2. Production of membrane proteins for diagnostic or screening assays.
  - 3. Production of membrane proteins for biochemical studies.
  - 4. Production of membrane protein for structural studies.
  - 5. Antigen production for generation of antibodies for immuno-histochemical mapping, including mapping of orphan receptors and ion channels.

Also provided by the present invention is a eukaryotic host cell transfected according to any of the preceding transfection methods. Preferably, the eukaryotic host cell is a mammalian host cell line.

As already described, example of useful mammalian host cell lines include human cells such as human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol 36, 59 (1977)), human cervical carcinoma cells (HELA, ATCC CCL 2), human lung cells (W138, ATCC CCL 75), human liver cells (Hep G2, HB 8065); rodent cells such as baby hamster kidney cells (BHK, ATCC CCL 10), Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, *Proc. Natl. Acad. Sci. USA*, 77, 4216 (1980)), mouse sertoli cells (TM4, Mather, *Biol. Reprod* 23, 243-251 (1980)), mouse mammary tumor (MMT 060562, ATCC CCL51);

and cells from other mammals such as monkey kidney CV1 line transformed by SV4O
 (COS-7, ATCC CRL 1651); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); myeloma (e.g. NS0) /hybridoma cells.

Most preferred for uses herein are CHO cells.

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The present invention also provides for a cell transfection mixture or Kit comprising at least one purified and isolated DNA sequence according to the invention.

The invention further comprises a transgenic organism wherein at least some of its cells have stably incorporated at least one DNA sequence of

- a purified and isolated DNA sequence having protein production increasing activity,
- a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter,

- the sequences SEQ ID Nos 1 to 27,

- a purified and isolated cLysMAR element and/or fragment,
- a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences,
- a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants. Preferably, some of the cells of the transgenic organisms have been transfected according the methods described herein.
- Also envisioned in the present invention is a transgenic organism wherein its genome has stably incorporated at least one DNA sequence of
  - a purified and isolated DNA sequence having protein production increasing activity.
  - a purified and isolated MAR DNA sequence identifiable according to the method for identifying a MAR sequence using the described bioinformatic tool, the combined method or the method comprising at least one filter,
  - the sequences SEQ ID Nos 1 to 27,
  - a purified and isolated cLysMAR element and/or fragment,
  - a synthetic MAR sequence comprising natural MAR element and/or fragments assembled between linker sequences,

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.

Transgenic eukaryotic organisms which can be useful for the present invention are for example selected form the group comprising mammals (mouse, human, monkey etc) and in particular laboratory animals such as rodents in general, insects (drosophila,

etc), fishes (zebra fish, etc.), amphibians (frogs, newt, etc..) and other simpler organisms such as c. elegans, yeast, etc....

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Yet another object of the present invention is to provide a computer readable medium comprising computer-executable instructions for performing the method for identifying a MAR sequence as described in the present invention.

The foregoing description will be more fully understood with reference to the following Examples. Such Examples, are, however, exemplary of methods of practising the present invention and are not intended to limit the scope of the invention.

### **EXAMPLES**

## Example 1: SMAR Scan® and MAR sequences

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A first rough evaluation of SMAR Scan® was done by analyzing experimentally defined human MARs and non-MAR sequences. As MAR sequences, the previous results from the analysis of human MARs from SMARt Db were used to plot a density histogram for each criterion as shown in Fig. 1. Similarly, non-MAR sequences were also analyzed and plotted. As non-MAR sequences, all Ref-Seq-contigs from the chromosome 22 were used, considering that this latter was big enough to contain a negligible part of MAR sequences regarding the part of non-MAR sequences.

The density distributions shown in Fig. 1 are all skewed with a long tail. For the highest bend, the highest major groove depth and the highest minor groove width, the distributions are right skewed. For the lowest melting temperature, the distributions are left-skewed which is natural given the inverse correspondence of this criterion regarding the three others. For the MAR sequences, biphasic distributions with a second weak peak, are actually apparent. And between MAR and non-MAR sequences distributions, a clear shift is also visible in each plot.

Among all human MAR sequences used, in average only about 70% of them have a value greater than the 75th quantile of human MARs distribution, this for the four different criteria. Similarly concerning the second weak peak of each human MARs distribution, only 15% of the human MAR sequences are responsible of these outlying values. Among these 15% of human MAR sequences, most are very well documented MARs, used to insulate transgene from position effects, such as the interferon locus MAR, the beta-globin locus MAR (Ramezani A, Hawley TS, Hawley RG, "Performanceand safety-enhanced lentiviral vectors containing the human interferon-beta scaffold attachment region and the chicken beta-globin insulator", Blood, 101:4717-4724, 2003), or the apolipoprotein MAR (Namciu, S, Blochinger KB, Fournier REK, "Human matrix attachment regions in-sulate transgene expression from chromosomal position effects in Drosophila melanogaster", Mol. Cell. Biol., 18:2382-2391, 1998). Always with the same data, human MAR sequences were also used to determine the association between the four theoretical structural properties computed and the ATcontent. Fig. 2 represents the scatterplot and the corresponding correlation coefficient r for every pair of criteria.

## Example 2: Distribution plots of MAR sequences by organism

MAR sequences from SMARt DB of other organisms were also retrieved and analyzed similarly as explained previously. The MAR sequences density distributions for the mouse, the chicken, the sorghum bicolor and the human are plotted jointly in Fig. 3.

### 45 Example 3: MAR prediction of the whole chromosome 22

All RefSeq contigs from the chromosome 22 were analyzed by SMAR Scan® using the default settings this time. The result is that SMAR Scan® predicted a total of 803 MARs, their average length being 446 bp, which means an average of one MAR predicted per 42 777 bp. The total length of the predicted MARs corresponds to 1% of the chromosome 22 length. The AT-content of the predicted regions ranged from

WO 2005/040377 PCT/EP2004/011974 65,1% to 93.3%; the average AT-content of all these regions being 73.5%. Thus,

65,1% to 93.3%; the average AT-content of all these regions being 73.5%. Thus, predicted MARs were AT-rich, whereas chromosome 22 is not AT-rich (52.1% AT).

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SMARTest was also used to analyze the whole chromosome 22 and obtained 1387 MAR candidates, their average length being 494 bp representing an average of one MAR predicted per 24 765 bp. The total length of the predicted MARs corresponds to 2% of the chromosome 22. Between all MARs predicted by the two softwares, 154 predicted MARs are found by both programs, which represents respectively 19% and 11% of SMAR Scan® and SMARTest predicted MARs. Given predicted MARs mean length for SMAR Scan® and SMARTest, the probability to have by chance an overlapping between SMAR Scan® and SMARTest predictions is 0.0027% per prediction.

To evaluate the specificity of SMAR Scan® predictions, SMAR Scan® analyses were performed on randomly shuffled sequences of the chromosome 22 (Fig. 4). Shuffled sequences were generated using 4 different methods: by a segmentation of the chromosome 22 into nonoverlapping windows of 10 bp and by separately shuffling the nucleotides in each window; by "scrambling" which means a permutation of all nucleotides of the chromosome; by "rubbling" which means a segmentation of the chromosome in fragments of 10 bp and a random assembling of these fragments and finally by order 1 Markov chains, the different states being the all the different DNA dinucleotides and the transition probabilities between these states being based on the chromosome 22 scan. For each shuffling method, five shuffled chromosome 22 were generated and analyzed by SMAR Scan® using the default settings. Concerning the number hits, an average of 3 519 170 hits (sd: 18 353) was found for the permutated chromosome 22 within nonoverlapping windows of 10 bp, 171 936,4 hits (sd: 2 859,04) for the scrambled sequences and 24 708,2 hits (sd: 1 191,59) for the rubbled chromosome 22 and 2 282 hits in average (sd: 334.7) for the chromosomes generated according to order 1 Markov chains models of the chromosome 22, which respectively represents 185% (sd: 0.5% of the mean), 9% (sd: 1.5%), 1% (sd: 5%) and 0.1% (sd: 15%) of the number of hits found with the native chromosome 22. For the number of MARs predicted, which thus means contiguous hits of length greater than 300, 1 997 MARs were predicted with the shuffled chromosome 22 within windows of 10 bp (sd: 31.2), only 2.4 MARs candidates were found in scrambled sequences (sd: 0.96) and none for the rubbled and for the sequences generated according to Markov chains model, which respectively represents 249% and less than 0.3% of the number of predicted MARs found with the native chromosome 22. These data provide indications that SMAR Scan® detects specific DNA elements which organization is lost when the DNA sequences are shuffled.

# Example 4: Analysis of known matrix attachment regions in the Interferon locus with SMAR Scan®

The relevance of MAR prediction by SMAR Scan® was investigated by analyzing the recently published MAR regions of the human interferon gene cluster on the short arm of chromosome 9 (9p22). Goetze et al. (already cited) reported an exhaustive analysis of the WP18A10A7 locus to analyze the suspected correlation between BURs (termed in this case stress-induced duplex destabilization or SIDD) and *in vitro* binding to the nuclear matrix (Fig. 9, lower part). Three of the SIDD peaks were in agreement with the *in vitro* binding assay, while others did not match matrix attachment sites. Inspection of the interferon locus with SMAR Scan® (Fig. 9, top part) indicated that three majors peaks accompanied by clusters of SATB1, NMP4 and MEF2 regulators binding sites

correlated well with the active MARs. Therefore, we conclude that the occurrence of predicted CUEs and binding sites for these transcription factors is not restricted to the *cLys*MAR but may be a general property of all MARs. These results also imply that the SMAR Scan® program efficiently detects MAR elements from genomic sequences.

# Example 5: Accuracy of SMAR Scan® prediction and comparison with other predictive tools

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The accuracy of SMAR Scan® was evaluated using six genomic sequences for which experimentally determined MARs have been mapped. In order to perform a comparison with other predictive tools, the sequences analyzed are the same with the sequences previously used to compare MAR-Finder and SMARTest. These genomic sequences are three plant and three human sequences (Table 1) totalizing 310 151 bp and 37 experimentally defined MARs. The results for SMARTest and MAR-Finder in Table 1 come from a previous comparison (Frisch M, Frech K, Klingenhoff A, Cartharius K, Liebich I and Werner T, In silico pre-diction of scaffold/matrix attachment regions in large genomic sequences, *Genome Research*, 12:349-354, 2001.). MAR-Finder has been used with the default parameters excepted for the threshold that has been set to 0.4 and for the analysis of the protamine locus, the AT-richness rule has been excluded (to detect the non AT-rich MARs as was done for the protamine locus).

W O 2003/040377					PC 1/EP2004/0
Sequence, description and reference	Length	Experiment- ally defined	SMARTest prediction	MAR-Finder prediction	SMAR Scan prediction
		MARs positions	positions	positions	positions
	(kb)	(kb)	(kb)	(kb)	(kb)
Oryza Sativa putative	30.034	0,0-1.2	-	-	
ADP-glucose pyro-	30.057	5.4-7.4	6.5-7.0	_	_
phosphorylase subunit			15.2-15.7	15.7-15.9	15,6-16
SH2 and putative			16.2-16.6	-	-
NADPH dependant		17.3-18.5	17.6-18.3	17.5-18.4	17.6-18.2
reductase À1 genes		20.0-23.1	19.6-20.1	19.8-20.4	21.6-22
(U70541), [4]			20.7-21.3	21.3-21.5	-
			23.6-23.9	23.9-24.2	23.4-23.8
			25.0-25.4	24.7-25.1	-
Sorghum bicolor ADP-	42.446	0.0-1.5	27.5-27.9	-	
glucose pyrophopho-	42.440	7.1-9.7	_	_	7.4-7.7
rylase subunit SH2,			21.3-21.9		21.5-21.8
NADPH-dependant		22.4-24.7	22.9-24.0	23.2-24.2	22.9-23.2
reducatse Å1-b genes			~	-	23.6-24.0
(AF010283), [4]			27.3-27.6	26.9-27.5	27.3-27.6
		32.5-33.7	-	· · · -	33.4-33.9
Sorghum bicolor BAC	78.195	41.6-42.3 ~0.9	-	-	-
clone 110K5	¥0.130	~5.8		_	
(AF124045), [37]		~6.3	_	_	_
₩		~9.3	-	-	-
		~15.0	15.1-15.8	-	-
		~18.5		-	
		√21.9	21.7-22.0	-	21.4-21.9
	1	~23.3 ~25.6	-	-	-
		~20.0 ~29.1	1 _	_	29.2-29.5
		~34.6	_		-
			-	<b>1</b> 20	39.0-40.0
		~44.1	44.1-44.5	-	
		~48.5	47.9-49.5	47.9-49.4	48.1-48.6
		0	-	-	48.8-49.3
		~57.9	60 4 60 7	-	-
1		∿62.9 √67.1	63.1-63.7	_	_
		~67.1 ~69.3	_		_
		~73.7	74.3-74.7	_	74.3-74.6
Human alpha-1-antitry-	30.461	2.6-6.3	5.5-6.0	3.0-3.2	5.4-5.8
sin and corticosteroid		00000		5.1-6.0	-
binding globulin		22.0-30.4	25.7-26.2	24.9-25.3	25.8-26.4
intergenic region (AF156545), [35]			27.5-27.8	25.5-25.8 26.2-26.4	_
(Ar 100040), [DD]			_	27.5-28.2	_
Human protamine locus	53.060	8.8-9.7	-	8.0-8.9*	-
(U15422). [24]		32.6-33.6	-	33.9-34.8*	-
		37.2-39.4	-	33.9-34.8*	-
Li mania hata alahin	75.955	51.8-53.0 1.5-3.0	-	_**	2.3-2.6
Human beta-globin locus	10.800	1.5-3.0 15.6-19.0	18.0-18.4	15.5-16.0	2.3-2.6 15.3-15.6
(U01317), [21]		10.0-10.0	= W-M* 10 M	18.0-18.4	10.0
χου (φ. (μ. (Δ. ()			34.4-34.9	a way a kort	-
1		44.7-52.7	-	50.6-50.8	-
			56.6-57.1	56.5-57.2	
		60.0-70.0	59.8-60.3	58.1-58.5	62.8-63.1
I			65.6-66.0	63.0-63.6	-

			67.6-67.9 68.8-69.1	68.7-69.3	66.3-66.7 -
Sum(kb)	310.151	at least 56.1	14.5	13.8	9.5
Total numbers : Average kb /predicted MAR		37	28 11.076	25 12.406	22 14.097
True positives [number of experimentally defined MAR found]			19[14]	20[12]	17[14]
False positives False negatives Specificity Sensitivity			9 23 19/28= 68% 14/37= 38%	5 25 20/25= 80% 12/37= 32%	5 23 17/22= 77% 14/37= 38%

Table 1: Evaluation of SMAR Scan® accuracy

- Six different genomic sequences, three plant and three human sequences, for which experimentally defined MARs are known, were analyzed with MAR-Finder, SMARTest and SMAR Scan®. True positive matches are printed in bold, minus (-) indicates false negative matches. Some of the longer experimentally defined MARs contained more than one in silico prediction, each of them was counted as true positive match.
- Therefore, the number of true in silico predictions is higher than the number of experimentally defined MARs found. Specificity is defined as the ratio of true positive predictions, whereas sensitivity is defined as the ratio of experimentally defined MARs found. \* AT-rich rule excluded using MAR-Finder.
- SMARTest predicted 28 regions as MARs, 19 (true positives) of these correlate with experimentally defined MARs (specificity: 68%) whereas 9 (32%) are located in non-MARs (false positives). As some of the longest experimentally determined MARs contains more than one in silico prediction, the 19 true positives correspond actually to 14 different experimentally defined MARs (sensitivity: 38%). MARFinder
   predicted 25 regions as MARs, 20 (specificity: 80%) of these correlate with experimentally defined MARs corresponding to 12 different experimentally defined MARs (sensitivity: 32%). SMAR Scan® predicted 22 regions, 17 being true positives (specificity: 77%) matching 14 different experimentally defined MARs (sensitivity: 38%).
- As another example, the same analysis has been applied to human chromosomes 1 and 2 and lead to the determination of 23 MARs sequences (SEQ ID N° 1 to 23). These sequences are listed in Annex 1 in ST25 format.

# Example 6: Analyses of the whole genome using the combined method (SMAR Scan®-pfsearch)

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In order to test the potential correlation between the structural features computed by SMAR Scan® and the S/MAR functional activity, the whole human genome has been analyzed with the combined method with very stringent parameters, in order to get sequences with the highest values for the theoretical structural features computed, which are called "super" S/MARs below. This was done with the hope to obtain predicted MAR elements with a very potential to increase transgene expression and recombinant protein production. The putative S/MARs hence harvested were first analyzed from the bioinformatics perpective in an attempt to characterize and classify them.

## 6.1 S/MARs predicted from the analysis of the whole human genome

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As whole human genome sequence, all human RefSeq (National Center for Biotechnology Information, The NCBI handbook [Internet]. Bethesda (MD): National Library of Medicine (US), Oct. Chapter 17, The Reference Sequence (RefSeq) Project, 2002 (Available from http://www.ncbi.nih.gov/entrez/query.fcgi?db=Books) contigs (release 5) were used and analyzed with the combined method, using SMAR Scan® as filter in the first level processing, employing default settings except for the highest bend cutoff value, whereas a stringent threshold of 4.0 degrees (instead of 3.202 degrees) has been used for the DNA bending criterion.

In the second level processing, predicted transcription factors binding have been sought in the sequences selected from the previous step without doing any filtering on these sequences.

The analysis by the combined method of the whole human genome came up with a total of 1757 putative "super" S/MARs representing a total of 1 065 305 bp (0.35% of the whole human genome). Table 2 shows for each chromosome: its size, its number of genes, its number of S/MARs predicted, its S/MARs density per gene and its kb per S/MAR. This table shows that there are very various gene densities per S/MAR predicted for the different chromosomes (standard deviation represents more than 50% of the mean of the density of genes per S/MAR predicted and the fold difference between the higher and the lower density of genes per S/MAR is 6,5). Table 2 also shows that the kb per S/MAR varies less that the density of genes per S/MAR (standard deviation represents 25% of the mean of kb per S/MAR and the fold difference between the higher and the lower kb per S/MAR is 3.2).

Chromosome	Number of genes per	Size of the chromosome	Number of S/MARs	Density of genes	Kb per S/MAR
	chromosome	(millions bp)	predicted	per S/MAR	
1	2544	230	85	29.9	2705
2	1772	241	143	12.3	1685
3	1406	198	101	13.9	1960
4	1036	190	118	8.7	1610
5	1233	180	116	10.6	1551
6	1247	170	94	13.2	1808
7	1383	160	179	7.7	1754
8	942	145	77	12.2	1883
9	1100	119	48	22.9	2479
10	1003	133	71	14.1	1873
11	1692	132	67	25.2	1970
12	1278	131	78	16.3	1679
13	506	97	70	7.2	1385
14	1168	88	36	32.4	2444 .
15	895	83	35	25.5	2371
16	1107	81	41	27	1975
17	1421	80	37	38.4	2162
18	396	75	51	7.7	1470
19	1621	56	36	45.02	1555
20	724	60	28	25.8	2142
21	355	34	18	19.7	1888
22	707	34	28	25.2	1214
x	1168	154	170	6.8	905
Y	251	25	30	8.3	833
Sum	26 955	3 050	1 757	457	433 12
Mean	1 123	127	73	19	1 804
Sd	510	72.8	45	10	462

Table 2: Number of S/MARs predicted per chromosome. The number of genes per chromosome

corresponds to the NCBI human genome statistics (Build 34 Version 3) (National Center for Biotechnology Information, The NCBI handbook [Internet]. Bethesda (MD): National Library of Medicine (US), Oct. Chapter 17, The Reference Sequence (RefSeq) Project, 2002 (Available from http://www.ncbi.nih.gov/entrez/query.fcgi?db=Books) based on GenBank annotations. Chromosome sizes are the sum of the corresponding human RefSeq (National Center for Biotechnology Information, The NCBI handbook [Internet]. Bethesda (MD): National Library of Medicine (US), Oct. Chapter 17, The Reference Sequence (RefSeq) Project, 2002 (Available from http://www.ncbi.nih.gov/entrez/query.fcgi?db=Books) (release 5) contig lengths

10 6.2 Bioinformatics analysis of "super" MARS for transcription factor binding sites

The 1757 predicted "super" S/MARs sequences obtained previously by SMAR Scan® were then analyzed for potential transcription factors binding sites. This has been achieved using RMatch Professional (Kel AE, Gossling E, Reuter I, Cheremushkin E, KelMargoulis OV, Wingender E, MATCH: A tool for searching transcription factor binding sites in DNA sequences, *Nucleic Acids Res.* 31(13):35769, 2003), a weight matrixbased tool based on TRANSFAC (Wingender E, Chen X, Fricke E, Geffers R, Hehl R, Liebich I, Krull M, Matys V, Michael H, Ohnhauser R, Pruss M, Schacherer F, Thiele S, Urbach S, The TRANSFAC system on gene expression regulation, *Nucleic Acids Research*, 29(1):2813, 2001). Match 2.0 Professional has been used with most of the default settings Match analysis was based on TRANSFAC Professional, release 8.2 (20040630). The sums of all transcription factors binding prediction on the 1757 sequences analyzed according to Match are in Table 3. Based on this table, only the transcription factors totalizing at least 20 hits over the 1757 sequences analyzed were considered for further analyses.

Hereafter are some of the human transcription factors that are the most often predicted to bind on the 1757 putative S/MAR sequences and their Match description: Cdc5 (cell division control protein 5) a transcriptional regulator/repressor, Nkx3A a homeodomain protein regulated by androgen, POU1F1 (pituitaryspecific positive transcription factor 1) which is specific to the pituitary and stimulates cells proliferation. Thus, in addition to SATB1, NMP4 and MEF2, other transcription factors can participate in the activity of MARs.

AP1	1	AR	2	Bach2	1	Brn2	1
C/EBP	20	C/EBPgamma	5	CDP CR3	1	COMP1	2
CREBP1	34	Cdc5	858	Cdx2	35	Evi1	472
FOX	78	FOXD3	79	FOXJ2	244	FOXP3	29
Freac7	272	GATA1	2	GATA3	142	GATA4	125
HFH1	12	HFH3	1	HLF	275	HNF1	337
HNF3alpha	23	HNF3beta	71	HP1	2	Lhx3	22
MEF2	114	MRF2	57	Myc	18	NKX3A	849
Nkx25	2	Oct1	191	PBX	5	POU1F1	483
POU3F2	11	POU6F1	29	Pax3	3	Pax6	20
Pit1	505	SRF	8	TEF	2852	TFIIA	14
TTF1	1	V\$MTATA_B	4	VBP	53	Vmw65	1
XFD1	65	XFD2	418	XFD3	2		

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Table 3 is a summary of all transcription factors binding prediction (totalizing 20 hits or more) on the 1757 sequences analyzed.

5 6.3 Bioinformatics analysis of predicted "super" MARs for dinucleotide frequencies

Various computer analysis were performed in order to easily identify "super" S/MAR sequences using an explicit criterion that could be identified without computing. Among those, a di-nucleotide analysis was performed on the 1757 superMARs, computing each of the 16 possible dinucleotide percentage for each sequence considering both strands in the 5' > 3' direction.

A summary (min., max., median, mean, 25th percentile and 75th percentile) as well as the histograms of each dinucleotide percentage over the 1757 S/MAR sequences are respectively presented in Table 4. A similar analysis was performed on randomly selected sequences from the human genome, representing randomly selected non-S/MAR sequences (which might however contain some MARs). Table 5 represents respectively a summary of the dinucleotide content analysis for these sequences.

Table 4: Dinucleotide percentages over the 1757 S/MAR sequences

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	AA %	AC %	AG %	AT %
Minimum	0.000	0.0000	0.0000	18.50
25th percentile	4.234	0.9372	0.1408	32.11
Median	7.843	2.2408	0.4777	34.68
Mean	7.184	3.2117	1.0865	34.32
75th percentile	10.110	4.7718	1.5096	36.94
Maximum	17.290	12.9479	8.1230	50.00
	CA %	CC %	CG %	CT %
Minimum	0.0000	0.00000	0.0000	0.0000
25th percentile	0.9695	0.00000	0.0000	0.1408
Median	1.9776	0.00000	0.0000	0.4777
Mean	2.6977	0.14123	0.2709	1.0865
75th percentile	3.7543	0.09422	0.1256	1.5096
Maximum	10.4061	4.24837	7.4410	8.1230
	GA %	GC %	GG %	GT %
Minimum	0.00000	0.0000	0.00000	0.0000
25th percentile	0.08696	0.0000	0.00000	0.9372
Median	0.32616	0.0000	0.00000	2.2408
Mean	0.63347	0.2104	0.14123	3.2117
75th percentile	0.83333	0.1914	0.09422	4.7718
Maximum	5.77889	9.8795	4.24837	12.9479
	TA %	TC %	TG %	TT %
Minimum	28.63	0.00000	0.0000	0.000
25th percentile	33.48	0.08696	0.9695	4.234
Median	35.22	0.32616	1.9776	7.843
Mean	35.29	0.63347	2.6977	7.184
75th percentile	37.14	0.83333	3.7543	10.110
Maximum	50.00	5.77889	10.4061	17.290

Considering the results of the predicted S/MAR elements and of the nonS/MAR sequences in the summary tables, noticeable differences can be noticed in the AT et TA dinucleotide contents between these two groups of sequences. AT and TA represent respectively at least 18,5 % and 28.6 % of the dinucleotide content of the predicted S/MAR sequences, whereas the minimum percentages for the same dinucleotides in

nonS/MAR sequences are respectively 0.3 % and 0%. Similarly, the maximum CC and GG content in S/MAR sequences is 4.2 %, whereas in nonS/MAR sequences the percentages for these two dinucleotides can amount up to 20.8 %.

The correlation between AT and TA dinucleotide percentages and the DNA highest bend as computed by SMAR Scan® is depicted in Fig. 17 for the predicted S/MAR sequences and in Fig.18 for the nonS/MAR sequences. The different scatterplots of these figures show that the TA percentage correlates well with the predicted DNA bend as predicted by SMAR Scan®.

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Table 5: Dinucleotide percentages over the 1757 nonS/MAR sequences summary

	AA %	AC %	AG %	AT %
Minimum	0.000	1.735	1.512	0.3257
25th percentile	7.096	4.586	6.466	5.1033
Median	9.106	5.016	7.279	6.8695
Mean	8.976	5.054	7.184	7.0108
75th percentile	10.939	5.494	7.969	8.7913
Maximum	17.922	13.816	12.232	23.1788
	CA %	CC %	CG %	CT %
Minimum	3.571	0.8278	0.0000	1.512
25th percentile	6.765	4.1077	0.4727	6.466
Median	7.410	5.5556	0.8439	7.279
Mean	7.411	5.9088	1.2707	7.184
75th percentile	8.010	7.2460	1.5760	7.969
Maximum	15.714	20.8415	12.6074	12.232
	GA %	GC %	GG %	GT %
Minimum	1.319	0.4967	0.8278	1.735
25th percentile	5.495	3.2615	4.1077	4.586
Median	6.032	4.4092	5.5556	5.016
Mean	6.065	4.7468	5.9088	5.054
75th percentile	6.602	5.8824	7.2460	5.494
Maximum	10.423	16.0000	20.8415	13.816
	TA %	TC %	TG %	TT %
Minimum	0.000	1.319	3.571	0.000
25th percentile	3.876	5.495	6.765	7.096
Median	5.625	6.032	7.410	9.106
Mean	5.774	6.065	7.411	8.976 .
75th percentile	7.464	6.602	8.010	10.939
Maximum	24.338	10,423	15.714	17.922

Four of the novel super MARs were randomly picked and analyzed for AT and TA dinucleotide content, and compared with the previously known chicken lysMAR, considering windows of 100 base pairs (Table 6).

Surprinsigly, Applicants have shown that all of the super MARs have AT dinucleotide frequencies greater then 12%, and TA dinucleotides greater than 10% of the total dinucleotides analysed in a window of 100base pairs of DNA. The most efficient MARs display values around 34% of the two dinucleotide pairs.

Table 6. Summary of %AT and TA dinucleotide frequencies of experimentally verified MARs

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CLysMAR (average of CUEs)	AT%: 12.03	TA%: 10.29	SEQ ID No
P1 68	AT%: 33.78	TA%: 33.93	SEQ ID No
P1 6	AT%: 34.67	TA%: 34.38	SEQ ID No

P1 42	AT%: 35.65	TA%: 35.52	SEQ ID No
Mean value for all human "super"MARs	AT%: 34.32	TA%: 35.29	
Mean value for all human non-MARs	AT%: 7.01	TA%: 5.77	

## 6.4 Analysis of orthologous intergenic regions of human and mouse genomes

- In order to get an insight on S/MAR evolution, orthologous intergenic regions of human and mouse genomes have been analysed with SMAR Scan®. The data set used is composed of 87 pairs of complete orthologous intergenic regions from the human and mouse genomes (Shabalina SA, Ogurtsov AY, Kondrashov VA, Kondrashov AS, Selective constraint in intergenic regions of human and mouse genomes, *Trends*10 Genet, 17(7):3736, 2001) (average length ~12 000 bp) located on 12 human and on 12 mouse chromosomes, the synteny of these sequences was confirmed by pairwise
- Analysis of the 87 human and mouse orthologous intergenic sequences have been analysed with SMAR Scan® using its default settings. Analysis of the human sequences yielded a total of 12 S/MARs predicted (representing a total length of 4 750 bp), located on 5 different intergenic sequences.

sequence alignment and consideration of the annotations of the flanking genes

(experimental or predicted).

- 20 Among the three human intergenic sequences predicted to contain a "super" S/MAR using SMAR Scan® stringent settings, one of the corresponding mouse orthologous intergenic sequence is also predicted to contain a S/MAR (human EMBL ID: Z96050, position 28 010 to 76 951 othologous to mouse EMBL ID: AC015932, positions 59 884 to 89 963). When a local alignement of these two orthologous intergenic sequences is 25 performed, the best local alignement of these two big regions correspond to the regions predicted by SMAR Scan® to be S/MAR element. A manual search for the mouse orthologs of the two other human intergenic sequences predicted to contain a "super" S/MAR was performed using the Ensembl Genome Browser (http://ensembl.org). The mouse orthologous intergenic sequences of these two human sequences were retrieved using Ensembl orthologue predictions (based on gene names), searching the 30 orthologous mouse genes for the pairs of human genes flanking these intergenic regions.
- Because SMAR Scan® has been tuned for human sequences and consequently yields little "super"MARs with mouse genomic sequences, its default cutoff values were slightly relaxed for the minimum size of contiguous hits to be considered as S/MAR (using 200 bp instead of 300 bp). Analysis by SMAR Scan® of these mouse sequences predicted several S/MARs having high values for the different computed structural features. This finding suggests that the human MAR elements are conserved across species.

### Example 7: Dissection of the chicken lysozyme gene 5'- MAR

The 3000 base pair 5'-MAR was dissected into smaller fragments that were monitored for effect on transgene expression in Chinese hamster ovary (CHO) cells. To do so, seven fragments of ~400 bp were generated by polymerase chain reaction (PCR). These PCR-amplified fragments were contiguous and cover the entire MAR sequence when placed end-to-end. Four copies of each of these fragments were ligated in a head-to-tail orientation, to obtain a length corresponding to approximately half of that of

the natural MAR. The tetramers were inserted upstream of the SV40 promoter in pGEGFPControl, a modified version of the pGL3Control vector (Promega). The plasmid pGEGFPControl was created by exchanging the luciferase gene of pGL3Control for the EGFP gene from pEGFP-N1 (Clontech). The 5'-MAR-fragment-containing plasmids thus created were co-transfected with the resistance plasmid pSVneo in CHO-DG44 cells using LipofectAmine 2000 (Invitrogen) as transfection reagent, as performed previously (Zahn-Zabal, M., et al., "Development of stable cell lines for production or regulated expression using matrix attachment regions" *J Biotechnol*, 2001. 87(1): p. 29-42.). After selection of the antibiotic (G-418) resistant cells, polyclonal cell populations were analyzed by FACS for EGFP fluorescence.

Transgene expression was expressed at the percentile of high expressor cells, defined as the cells which fluorescence levels are at least 4 orders of magnitude higher than the average fluorescence of cells transfected with the pGEGFPControl vector without MAR. Fig. 5 shows that multimerized fragments B, K and F enhance transgene expression, despite their shorter size as compared to the original MAR sequence. In contrast, other fragments are poorly active or fully inactive.

## Example 8: Specificity of B, K and F regions in the MAR context

The 5'-MAR was serially deleted from the 5'-end (Fig.6, upper part) or the 3'-end (Fig.6, lower part), respectively. The effect of the truncated elements was monitored in an assay similar to that described in the previous section. Figure 6 shows that the loss of ability to stimulate transgene expression in CHO cells was not evenly distributed.

In this deletion study, the loss of MAR activity coincided with discrete regions of transition which overlap with the 5'-MAR B-, K- and F-fragment, respectively. In 5' deletions, activity was mostly lost when fragment K and F were removed. 3' deletions that removed the F and b elements had the most pronounced effects. In contrast, flanking regions A, D, E and G that have little or no ability to stimulate transgene expression on their own (Fig. 5), correspondingly did not contribute to the MAR activity in the 5'- and 3'-end deletion studies (Fig. 6).

### **Example 9:Structure of the F element**

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The 465 bp F fragment was further dissected into smaller sub-fragments of 234, 243, 213 bp and 122, 125 and 121 bp, respectively. Fragments of the former group were octamerized (8 copies) in a head-to-tail orientation, while those of the latter group were similarly hexa-decamerized (16 copies), to maintain a constant length of MAR sequence. These elements were cloned in pGEGFPControl vector and their effects were assayed in CHO cells as described previously. Interestingly, fragment FIII retained most of the activity of the full-length F fragment whereas fragment FII, which contains the right-hand side part of fragment FIII, lost all the ability to stimulate transgene expression (Fig. 7). This points to an active region comprised between nt 132 and nt 221 in the FIB fragment. Consistently, multiple copies of fragments FI and FIB, which encompass this region, displayed similar activity. FIIA on its own has no activity. However, when added to FIB, resulting in FIII, it enhances the activity of the former. Therefore FIIA appears to contain an auxiliary sequence that has little activity on its own, but that strengthens the activity of the minimal domain located in FIB.

Analysis of the distribution of individual motifs within the lysozyme gene 5'-MAR is shown in Fig. 8 A, along with some additional motifs that we added to the analysis. Most of these motifs were found to be dispersed throughout the MAR element, and not

specifically associated with the active portions. For instance, the binding sites of transcription factors and other motifs that have been associated with MARs were not preferentially localized in the active regions. It has also been proposed that active MAR sequences may consist of combination of distinct motifs. Several computer programs (MAR Finder, SMARTest, SIDD duplex stability) have been reported to identify MARs as regions of DNA that associate with the DNA matrix. They are usually based on algorithms that utilizes a predefined series of sequence-specific patterns that have previously been suggested as containing MAR activity, as exemplified by MAR Finder, now known as MAR Wiz. The output of these programs did not correlate well with the transcriptionally active portions of the *cLysMAR*. For instance, peaks of activity obtained with MAR Finder did not clearly match active MAR sub-portion, as for instance the B fragment is quite active in vivo but scores negative with MAR Finder (Fig. 8B, compare the top and middle panels). Bent DNA structures, as predicted by this program, did not correlate well either with activity (Fig. 8B, compare the top and bottom panels). Similar results were obtained with the other available programs (data not shown).

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The motifs identified by available MAR prediction computer methods are therefore unlikely to be the main determinants of the ability of the *cLysMAR* to increase gene expression. Therefore, a number of other computer tools were tested. Surprisingly, predicted nucleosome binding sequences and nucleosome disfavouring sequences were found to be arranged in repetitively interspersed clusters over the MAR, with the nucleosome favouring sites overlapping the active B, K and F regions. Nucleosome positioning sequences were proposed to consist of DNA stretches that can easily wrap around the nucleosomal histones, and they had not been previously associated with MAR sequences.

Nucleosome-favouring sequences may be modelled by a collection of DNA features that include moderately repeated sequences and other physico-chemical parameters that may allow the correct phasing and orientation of the DNA over the curved histone surface. Identification of many of these DNA properties may be computerized, and up to 38 different such properties have been used to predict potential nucleosome positions. Therefore, we set up to determine if specific components of nucleosome prediction programs might correlate with MAR activity, with the objective to construct a tool allowing the identification of novel and possibly more potent MARs from genomic sequences.

To determine whether any aspects of DNA primary sequence might distinguish the active B, K and F regions from the surrounding MAR sequence, we analyzed the 5'-MAR with MAR Scan®. Of the 38 nucleosomal array prediction tools, three were found to correlate with the location of the active MAR sub-domains (Fig. 9A). Location of the MAR B, K and F regions coincides with maxima for DNA bending, major groove depth and minor groove width. A weaker correlation was also noted with minima of the DNA melting temperature, as determined by the GC content. Refined mapping over the MAR F fragment indicated that the melting temperature valley and DNA bending summit indeed correspond the FIB sub-fragment that contains the MAR minimal domain (Fig. 9B). Thus active MAR portions may correspond to regions predicted as curved DNA regions by this program, and we will refer to these regions as CUE-B, CUE-K and CUE-F in the text below. Nevertheless, whether these regions correspond to actual bent DNA and base-pair unwinding regions is unknown, as they do not correspond to bent DNA as predicted by MAR Wiz (Fig.9B).

Example 10: Imprints of other regulatory elements in the F fragment

Nucleosome positioning features may be considered as one of the many specific chromatin codes contained in genomic DNA. Although this particular code may contribute to the activity of the F region, it is unlikely to determine MAR activity alone. as the 3' part of the F region enhanced activity of the minimal MAR domain contained in the FIB portion. Using the MatInspector program (Genomatix), we searched for transcription factor binding sites with scores higher than 0.92 and found DNA binding sequences for the NMP4 and MEF2 proteins in the 3' part of the F fragment (Fig. 8B). To determine whether any of these transcription factor-binding sites might localize close to the B and K active regions, the entire 5'-MAR sequence was analyzed for binding by NMP4 and MEF2 and proteins reported to bind to single-stranded or double-stranded form of BURs, Among those, SATB1 (special AT-rich binding protein 1) belongs to a class of DNA-binding transcription factor that can either activate or repress the expression of nearby genes. This study indicated that specific proteins such as SATB1, NMP4 (nuclear matrix protein 4) and MEF2 (myogenic enhancer factor 2), have a specific distribution and form a framework around the minimal MAR domains of cLysMAR (Fig. 10). The occurrence of several of these NMP4 and SATB1 binding sites has been confirmed experimentally by the EMSA analysis of purified recombinant proteins (data not shown).

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# Example 11 : Construction of artificial MARs by combining defined genetic elements

To further assess the relative roles of the various MAR components, the *cLysMAR* was deleted of all three CUE regions (Fig. 11, middle part), which resulted in the loss of part of its activity when compared to the complete MAR sequence similarly assembled from all of its components as a control (Fig. 11, top part). Consistently, one copy of each CUE alone, or one copy of each of the three CUEs assembled head-to-tail, had little activity in the absence of the flanking sequences. These results strengthen the conclusion that optimal transcriptional activity requires the combination of CUEs with of flanking sequences. Interestingly, the complete MAR sequence generated from each of its components, but containing also BgIII-BamHI linker sequences (AGATCC) used to assemble each DNA fragment, displayed high transcriptional activity (6 fold activation) as compared to the 4.8 fold noted for the original MAR element in this series of assays (see Fig. 5).

We next investigated whether the potentially curved DNA regions may also be active in an environment different from that found in their natural MAR context. Therefore, we set up to swap the CUE-F, CUE-B and CUE-K elements, keeping the flanking sequences unchanged. The sequences flanking the CUE-F element were amplified by PCR and assembled to bracket the various CUEs, keeping their original orientation and distance, or without a CUE. These engineered ~1.8 kb MARs were then assayed for their ability to enhance transgene expression as above. All three CUE were active in this context. and therefore there action is not restricted to one given set of flanking sequences. Interestingly, the CUE-K element was even more active than CUE-F when inserted between the CUE-F flanking sequences, and the former composite construct exhibited an activity as high as that observed for the complete natural MAR (4.8 fold activation). What distinguishes the CUE-K element from CUE-F and CUE-B is the presence of overlapping binding sites for the MEF-2 and SatB1 proteins, in addition to its CUE feature. Therefore, fusing CUE-B with CUE-F-flanking domain results in a higher density of all three binding sites, which is likely explanation to the increased activity. These results indicate that assemblies of CUEs with sequences containing binding sites

for proteins such as NMP4, MEF-2, SatB1, and/or polyPpolyQ proteins constitute potent artificial MAR sequences.

### **Example 12: Expression vectors**

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Three expression vectors according to the present invention are represented on Figure 12.

**Plasmid pPAG01** is a 5640 bp pUC19 derivative. It contains a 2960 bp chicken DNA fragment cloned in *BamH1* and *XbaI* restriction sites. The insert comes from the border of the 5'-end of the chicken lyzozyme locus and has a high A/T-content.

**Plasmid pGEGFP** (also named pSV40EGFP) control is a derivative of the pGL3-control vector (Promega) in which the luciferase gene sequence has been replaced by the EGFP gene sequence form the pEGFP-N1 vector (Clontech). The size of pGEGFP plasmid is 4334bp.

Plasmid pUbCEGFP control is a derivative of the pGL3 wit an Ubiquitin promoter.

Plasmid pPAG01GFP (also named pMAR-SV40EGFP) is a derivative of pGEGFP with the 5'-Lys MAR element cloned in the MCS located just upstream of the SV40 promoter. The size of the pPAG01EGF plasmid is 7285bp.

# Example 13 ; Effect of the additional transfection of primary transfectant cells on transgene expression

- One day before transfection, cells were plated in a 24-well plate, in growth medium at a density of 1.35 x 10<sup>5</sup> cells/well for CHO-DG44 cells. 16 hours post-inoculum, cells were transfected when they reached 30-40% confluence, using Lipofect-AMINE 2000 (hereinafter LF2000), according to the manufacturer's instructions (Invitrogen). Twenty-seven microliters of serum free medium (Opti-MEM; Invitrogen) containing 1.4 µl of
- LF2000 were mixed with 27 μl of Opti-MEM containing 830 ng of linear plasmid DNA. The antibiotic selection plasmid (pSVneo) amounted to one tenth of the reporter plasmid bearing the GFP transgene. The mix was incubated at room temperature for 20 min, to allow the DNA-LF2000 complexes to form. The mixture was diluted with 300 μl of Opti-MEM and poured into previously emptied cell-containing wells. Following 3
- hours incubation of the cells with the DNA mix at 37°C in a CO<sub>2</sub> incubator, one ml of DMEM-based medium was added to each well. The cells were further incubated for 24 hours in a CO<sub>2</sub> incubator at 37°C. The cells were then transfected a second time according to the method described above, except that the resistance plasmid carried another resistance gene (pSVpuro). Twenty-four hours after the second transfection,
- cells were passaged and expanded into a T-75 flask containing selection medium supplemented with 500 µg/ml G-418 and 5 µg/ml puromycin. After a two week selection period, stably transfected cells were cultured in 6-well plates. Alternatively, the cell population was transfected again using the same method, but pTKhygro (Clontech) and pSVdhfr as resistance plasmids. The expression of GFP was analysed with
- 45 Fluorescence-activated cell sorter (FACS) and with a Fluoroscan.

Fig.13 shows that the phenotype of the twice-transfected cells (hereafter called secondary transfectants) not only was strongly coloured, such that special bulb and filter were not required to visualize the green color from the GFP protein, but also contained a majority of producing cells (bottom right-hand side FACS histogram) as compared to the parental population (central histogram). This level of fluorescence corresponds to specific cellular productivities of at least 10 pg per cell per day. Indeed,

cells transfected only one time (primary transfectants) that did not express the marker protein were almost totally absent from the cell population after re-transfection. Bars below 10<sup>1</sup> units of GFP fluorescence amounted 30% in the central histogram and less than 5% in the right histogram. This suggested that additional cells had been transfected and successfully expressed GFP.

Strikingly, the amount of fluorescence exhibited by re-transfected cells suggested that the subpopulation of cells having incorporated DNA twice expressed much more GFP than the expected two-fold increase. Indeed, the results shown in Table 2 indicate that the secondary transfectants exhibited, on average, more than the two-fold increase of GFP expected if two sets of sequences, one at each successive transfection, would have been integrated independently and with similar efficiencies. Interestingly, this was not dependent on the promoter sequence driving the reporter gene as both viral and cellular promoter-containing vectors gave a similar GFP enhancement (compare lane 1 and 2). However, the effect was particularly marked for the MAR-containing vector as compared to plasmids without MAR- (lane 3), where the two consecutive transfections resulted in a 5.3 and 4.6 fold increase in expression, in two distinct experiments.

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Type of plasmids	Primary transfection	Secondary transfection	EGFP fluorescence Fold increase
pUbCEGFP	4'992	14'334	2.8
pSV40EGFP	4'324	12'237	2.8
pMAR-SV40EGFP	6'996	36'748	5.3

Type of plasmids	Primary	Secondary	EGFP fluorescence	
	transfection	transfection	Fold increase	
pUbCEGFP	6'452	15'794	2.5	
pSV40EGFP	4'433	11'735	2.6	
pMAR-SV40EGFP	8'116	37'475	4.6	

**Table 7.** Effect of re-transfecting primary transfectants at 24 hours interval on GFP expression. Two independent experiments are shown. The resistance plasmid pSVneo was co-transfected with various GFP expression vectors. One day post-transfection, cells were re-transfected with the same plasmids with the difference that the resistance plasmid was changed for pSVpuro. Cells carrying both resistance genes were selected on 500 μg/ml G-418 and 5μg/ml puromycin and the expression of the reporter gene marker was quantified by Fluoroscan. The fold increases correspond to the ratio of fluorescence obtained from two consecutive transfections as compared to the sum of fluorescence obtained from the corresponding

independent transfections. The fold increases that were judged significantly higher are shown in bold, and correspond to fluorescence values that are consistently over 2-fold higher than the addition of those obtained from the independent transfections.

The increase in the level of GFP expression in multiply tranfected cells was not expected from current knowledge, and this effect had not been observed previously.

Taken together, the data presented here support the idea that the plasmid sequences that primarily integrated into the host genome would facilitate integration of other plasmids by homologous recombination with the second incoming set of plasmid molecules. Plasmid recombination events occur within a 1-h interval after the plasmid DNA has reached the nucleus and the frequency of homologous recombination

between co-injected plasmid molecules in cultured mammalian cells has been shown to be extremely high, approaching unity (Folger, K.R., K. Thomas, and M.R. Capecchi, Nonreciprocal exchanges of information between DNA duplexes coinjected into mammalian cell nuclei. Mol Cell Biol, 1985. 5(1): p. 59-69], explaining the integration of multiple plasmid copies. However, homologous recombination between newly introduced DNA and its chromosomal homolog normally occurs very rarely, at a frequency of 1 in 10<sup>3</sup> cells receiving DNA to the most [ Thomas, K.R., K.R. Folger, and M.R. Capecchi, High frequency targeting of genes to specific sites in the mammalian genome. Cell, 1986. 44(3): p. 419-28.]. Thus, the results might indicate that the MAR element surprisingly acts to promote such recombination events. MARs would not only modify the organization of genes in vivo, and possibly also allow DNA replication in conjunction with viral DNA sequences, but they may also act as DNA recombination signals.

# 15 <u>Example 14 : MARs mediate the unexpectedly high levels of expression in</u> multiply transfected cells

If MAR-driven recombination events were to occur in the multiple transfections process, we expect that the synergy between the primary and secondary plasmid DNA would be affected by the presence of MAR elements at one or both of the transfection steps. We examined this possibility by multiply transfections of the cells with pMAR alone or in combination with various expression plasmids, using the method described previously. Table 3 shows that transfecting the cells twice with the pMAR-SV40EGFP plasmid gave the highest expression of GFP and the highest degree of enhancement of all conditions (4.3 fold). In contrast, transfecting twice the vector without MAR gave little or no enhancement, 2.8-fold, instead of the expected two-fold increase. We conclude that the presence of MAR elements at each transfection step is necessary to achieve the maximal protein synthesis.

Table 8

Primary transfection		Secondary transfection				
Type of plasmid	EGFP-	Type of plasmid	EGFP-	Fold		
	fluorescence		fluorescence	increase		
pMAR	0	pMAR	0	0		
		pSV40EGFP	15'437	2.3-2.5		
		pMAR-SV40EGFP	30'488	2.6-2.7		
pMAR-SV40EGFP	11'278	pMAR-SV40EGFP	47'027	4.3-5.3		
		pMAR	12'319	1.0-1.1		
pSV40EGFP	6'114	pSV40EGFP	17'200	2.8		
		pMAR	11'169	1.8-2.3		

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Interestingly, when cells were first transfected with pMAR alone, and then retransfected with pSV40EGFP or pMAR-SV40EGFP, the GFP levels were more than doubled as compared to those resulting from the single transfection of the later plasmids (2.5 and 2.7 fold respectively, instead of the expected 1-fold). This indicates that the prior transfection of the MAR can increase the expression of the plasmid used in the second transfection procedure. Because MARs act only locally on chromatin structure and gene expression, this implies that the two types of DNA may have integrated at a similar chromosomal locus. In contrast, transfecting the GFP expression vectors alone, followed by the MAR element in the second step, yielded little or no improvement of the GFP levels. This indicates that the order of plasmid

transfection is important, and that the first transfection event should contain a MAR element to allow significantly higher levels of transgene expression.

If MAR elements favoured the homologous recombination of the plasmids remaining in episomal forms from the first and second transfection procedures, followed by their co-integration at one chromosomal locus, one would expect that the order of plasmid transfection would not affect GFP levels. However, the above findings indicate that it is more favourable to transfect the MAR element in the first rather than in the second transfection event. This suggests the following molecular mechanism: during the first transfection procedure, the MAR elements may concatemerize and integrate, at least in part, in the cellular chromosome. This integrated MAR DNA may in turn favour the further integration of more plasmids, during the second transfection procedure, at the same or at a nearby chromosomal locus.

### 15 Example 15: MARs as long term DNA transfer facilitators

If integrated MARs mediated a persistent recombination-permissive chromosomal structure, one would expect high levels of expression even if the second transfection was performed long after the first one, at a time when most of the transiently introduced episomal DNA has been eliminated. To address this possibility, the cells from Table 3, selected for antibiotic resistance for three weeks, were transfected again once or twice and selected for the incorporation of additional DNA resistance markers. The tertiary, or the tertiary and quaternary transfection cycles, were performed with combinations of pMAR or pMAR-SV40EGFP, and analyzed for GFP expression as before.

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Table 9

Tertiary transfection		Quaternary transfection			
Type of plasmid	EGFP- fluorescence	Fold increase	Type of plasmid	EGFP- fluorescence	Fold increas e
pMAR	18368	2.2	pMAR pMAR- SV40EGFP	43'186 140'000	2.4 7.6
pMAR-SV40EGF	16544	2.0	pMAR- SV40EGFP pMAR	91'000 33'814	5.5 2.0

**Table 9.** MARs act as facilitator of DNA integration.

The pMAR-SV40EGFP/ pMAR-SV40EGFP secondary transfectants were used in a third cycle of transfection at the end of the selection process. The tertiary transfection was accomplished with pMAR or pMAR-SV40EGFP, and pTKhygro as selection plasmid, to give tertiary transfectants. After 24 hours, cells were transfected again with either plasmid and pSVdhfr, resulting in the quaternary transfectants which were selected in growth medium containing 500  $\mu$ g/ml G-418 and  $5\mu$ g/ml puromycin, 300  $\mu$ g/ml hygromycin B and  $5\mu$ M methotrexate. The secondary transfectants initially exhibited a GFP fluorescence of 8300. The fold increases correspond to the ratio of fluorescence obtained from two consecutive transfections as compared to the sum of

fluorescence obtained from the corresponding independent transfections. The fold increases that were judged significantly higher are shown in bold, and correspond to fluorescence values that are 2-fold higher than the addition of those obtained from the independent transfections.

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These results show that loading more copies of pMAR or pMAR-SV40EGFP resulted in similar 2-fold enhancements of total cell fluorescence. Loading even more of the MAR in the quaternary transfection further enhanced this activity by another 2.4-fold. This is consistent with our hypothesis that newly introduced MAR sequences may integrate at the chromosomal transgene locus by homologous recombination and thereby further increase transgene expression.

When the cells were transfected a third and fourth time with the pMAR-SV40EGFP plasmid, GFP activity further increased, once again to levels not expected from the addition of the fluorescence levels obtained from independent transfections. GFP expression reached levels that resulted in cells visibly glowing green in day light (Fig. 14). These results further indicate that the efficiency of the quaternary transfection was much higher than that expected from the efficacy of the third DNA transfer. indicating that proper timing between transfections is crucial to obtain the optimal gene expression increase, one day being preferred over a three weeks period. We believe that MAR elements favour secondary integration events in increasing recombination frequency at their site of chromosomal integration by relaxing closed chromatin structure, as they mediate a local increase of histone acetylation (Yasui, D., et al., SATB1 targets chromatin remodelling to regulate genes over long distances. Nature, 2002. 419(6907): p. 641-5.]. Alternatively, or concomitantly, MARs potentially relocate nearby genes to subnuclear locations thought to be enriched in trans-acting factors, including proteins that can participate in recombination events such as topoisomerases. This can result in a locus in which the MAR sequences can bracket the pSV40EGFP repeats, efficiently shielding the transgenes from chromatin-mediated silencing effects.

# Example 16: Use of MARs identified with SMAR Scan® II to increase the expression of a recombinant protein.

35 Four MAR elements were randomly selected from the sequences obtained from the analysis of the complete human genome sequence with SMAR Scan® or the combined method. These are termed 1 6, 1 42, 1 68, (where the first number represents the chromosome from which the sequence originates, and the second number is specific to the predicted MAR along this chromosome) and X\_S29, a "super" MAR identified on chromosome X. These predicted MARs were inserted into the 40 pGEGFPControl vector upstream of the SV40 promoter and enhancer driving the expression of the green fluorescent protein and these plasmids were transfected into cultured CHO cells, as described previously (Zahn-Zabai, M., et al., Development of stable cell lines for production or regulated expression using matrix attachment regions. 45 J Biotechnol, 2001. 87(1): p. 29-42). Expression of the transgene was then analyzed in the total population of stably transfected cells using a fluorescent cell sorter (FACS) machine. As can be seen from Fig. 19, all of these newly identified MARs increased the expression of the transgene significantly above the expression driven by the chicken lysosyme MAR, the "super" MAR X S29 being the most potent of all of the newly 50 identified MARs.

# Example 17: Effect on hematocrit of *in vivo* expression of mEpo by electrotransfer of Network system with and without Human MAR (1-68).

The therapeutic gene encodes EPO (erythropoietin), an hormone used for the treatment of anemia. The EPO gene is placed under the control of a doxycycline inducible promoter, in a gene switch system described previously called below the Network system (Imhof, M. O., Chatellard, P., and Mermod, N. (2000). A regulatory network for efficient control of transgene expression. J. Gene. Med. 2, 107-116.). The EPO and regulatory genes are then injected in the muscle of mice using an *in vivo* electroporation procedure termed the electrotransfer, so that the genes are transferred to the nuclei of the muscle fibers. When the doxycycline antibiotic is added to the drinking water of the mice, this compound is expected to induce the expression of EPO, which will lead to the elevation of the hematocrit level, due to the increase in red blood cell counts mediated by the high levels of circulating EPO. Thus, if the MAR improved expression of EPO, higher levels of hematocrit would be expected.

In vivo experiments were carried out on 5 week-old C57BL6 female mice (Iffa Credo-Charles River, France). 30μg of plasmid DNA in normal saline solution was delivered by trans-cutaneous injections in the tibialis anterior muscle. All injections were carried out under Ketaminol (75 mg/kg) and Narcoxyl (10 mg/kg) anesthesia. Following the intramuscular injection of DNA, an electrical field was applied to the muscle. A voltage of 200 V/cm was applied in 8 ms pulses at 1Hz (Bettan M, Darteil R, Caillaud JM, Soubrier F, Delaere P, Branelec D, Mahfoudi A, Duverger N, Scherman D. 2000. "Highlevel protein secretion into blood circulation after electric pulse-mediated gene transfer into skeletal muscle". Mol Ther. 2: 204-10).

16 mice were injected by the Network system expressing EPO without the 1\_68 MAR and 16 other mice were injected with the Network system incorporating the MAR in 5' of the promoter/enhancer sequences driving the expression of the activator and EPO genes. In each group, half of the mice were submitted to doxycycline in drinking water from the beginning of the experiment (day 0 – the day of electrotransfer) and in the other half, doxycycline was put in drinking water starting at day 21.

35 Blood samples were collected using heparinated capillaries by retro-orbital punction at different times after the injection of plasmids. Capillaries were centrifugated 10 minutes at 5000 rpm at room temperature and the volumetric fraction of blood cells is assessed in comparison to the total blood volume and expressed as a percentile, determining the hematocrit level.

As can be deduced from Fig. 16 The group of mice injected by MAR-network, induced from the beginning of the experiment, display a better induction of the hematocrit in comparison of mice injected by original network without MAR. After 2 months, haematocrits in "MAR-containing group" is still at values higher (65%) than normal hematocrit levels (45-55%).

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More importantly, late induction (day 21) is possible only in presence of MAR but not from mice where the Network wwas injected without the MAR. Thus the MAR likely protects the transgenes from silencing and allows induction of its expression even after prolong period in non-inducing conditions.

Overall, the MAR element is able to increase the expression of the therapeutic gene as detected from its increased physiological effect on the hematocrit.

#### **CLAIMS**

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1. A purified and isolated DNA sequence having protein production increasing activity characterized in that said DNA sequence comprises

- a) at least one bent DNA element,
- b) and at least one binding site for a DNA binding protein.
- 2. The purified and isolated DNA sequence of claim 1 characterized in that the bent DNA element contains at least 10% of dinucleotide TA, and/or at least 12% of dinucleotide AT on a stretch of 100 contiguous base pairs.
  - 3. The purified and isolated DNA sequence of claim 2 characterized in that the bent DNA element contains at least 33% of dinucleotide TA, and/or at least 33% of dinucleotide AT on a stretch of 100 contiguous base pairs.
- 4. The purified and isolated DNA sequence of claims 1 to 2, characterized in that it comprises a MAR nucleotide sequence selected from the group comprising the sequences SEQ ID Nos 1 to 27, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
  - 5. The purified and isolated DNA sequence of claims 1 to 2, characterized in that it comprises a cLysMAR element and/or fragment, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
  - 6. The purified and isolated DNA sequence of claim 5, characterized in that said part thereof is a nucleotide sequence selected from the B, K and F regions.
- 7. The purified and isolated sequence of claims 1 to 6, characterized in that said DNA binding protein is a transcription factor.
- 8. The purified and isolated sequence of claim 7, characterized in that the transcription factor is selected from the group comprising the polyQpolyP domain proteins.
- The purified and isolated sequence of claim 7, characterized in that the transcription factor is selected from the group comprising SATB1, NMP4, MEF2, S8, DLX1, FREAC7, BRN2, GATA 1/3, TATA, Bright, MSX, AP1, C/EBP, CREBP1, FOX,
   Freac7, HFH1, HNF3alpha, Nkx25, POU3F2, Pit1, TTF1, XFD1, AR, C/EBPgamma, Cdc5, FOXD3, HFH3, HNF3 beta, MRF2, Oct1, POU6F1, SRF, V\$MTATA\_B, XFD2, Bach2, CDP CR3, Cdx2, FOXJ2, HFL, HP1, Myc, PBX, Pax3, TEF, VBP, XFD3, Brn2, COMP1, Evil, FOXP3, GATA4, HFN1, Lhx3, NKX3A, POU1F1, Pax6, TFIIA and Vmw65 or a combination of two or more of these transcription factors.
  - 10. A purified and isolated cLysMAR element and/or fragment having protein production increasing activity, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
  - 11. The cLysMAR element and/or fragment of claim 10 consisting of at least one nucleotide sequence selected from the B, K and F regions.

12. A synthetic MAR sequence comprising natural MAR elements and/or fragments assembled between linker sequences.

- 13. The synthetic MAR sequence of claim 12, characterized in that the MAR comprises a cLysMAR element and/or fragment, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- 14. The synthetic MAR sequence of claims 12 to 13, characterized in that the linker sequences are BgIII-BamHI linker.

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- 15. A method for identifying a MAR sequence using a Bioinformatic tool comprising the computing of values of one or more DNA sequence features corresponding to DNA bending, major groove depth and minor groove width potentials and melting temperature.
- 16. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 15, characterized in that said Bioinformatic tool contains algorithms, adapted to the use of profiles or weight-matrices, to compute values for one or more of said DNA sequence features corresponding to DNA bending, major groove depth and minor groove width potentials, and melting temperature.
- 17. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 16, characterized in that said profiles or weight-matrices are based on dinucleotide recognition.
  - 18. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 17, characterized in that said Bioinformatic tool computes values for all of said DNA sequence features.
  - 19. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 18, characterized in that said Bioinformatic tool is SMAR Scan®®.
- 20. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 15-19, characterized in that the identification of one or more DNA sequence features further comprises a feature corresponding to one or more binding sites for DNA binding proteins.
- 21. The method for identifying a MAR sequence using a Bioinformatic tool according 40 \* to claim 20, characterized in that said DNA binding protein is a transcription factor.
  - 22. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 21, characterized in that the transcription factor is selected from the group comprising polyQpolyP domain proteins or transcription factors.
- 23. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 20 to 21, characterized in that the DNA binding protein is selected from the group comprising SATB1, NMP4, MEF2, S8, DLX1, FREAC7, BRN2, GATA 1/3, TATA, Bright, MSX, AP1, C/EBP, CREBP1, FOX, Freac7, HFH1, HNF3alpha, Nkx25,
- POU3F2, Pit1, TTF1, XFD1, AR, C/EBPgamma, Cdc5, FOXD3, HFH3, HNF3 beta, MRF2, Oct1, POU6F1, SRF, V\$MTATA\_B, XFD2, Bach2, CDP CR3, Cdx2, FOXJ2, HFL, HP1, Myc, PBX, Pax3, TEF, VBP, XFD3, Brn2, COMP1, Evil, FOXP3, GATA4,

HFN1, Lhx3, NKX3A, POU1F1, Pax6, TFIIA and Vmw65 or a combination of two or more of these transcription factors.

- 24. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 15-23, characterized in that values for the identification of DNA bending are comprised between 3 to 5°.
- 25. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 24, characterized in that values for the identification of DNA bending are comprised between 3.8 to 4.4 °.
  - 26. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 15-25 characterized in that values for the identification of the major groove depth are comprised between 8.9 to 9.3 Å and values for the identification of minor groove width are comprised between 5.2 to 5.8 Å.

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- 27. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 26, characterized in that values for the identification of major groove depth are comprised between 9.0 to 9.3 Å and values for the identification of minor groove width are comprised between 5.4 to 5.7 Å.
  - 28. The method for identifying a MAR sequence using a Bioinformatic tool according to claims 15-27, characterized in that the melting temperature is comprised between 55 to 75 ° C.
- 29. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 28, characterized in that the melting temperature is comprised between 55 to 62 ° C.
- 30. The method for identifying a MAR sequence using a Bioinformatic tool of claims 15 to 29, characterized in that it further comprises at least one filter predicting DNA binding sites for DNA transcription factors.
- 31. The method for identifying a MAR sequence using a Bioinformatic tool according to claim 30, characterized in that the filter is applied before or after the Bioinformatic tool.
  - 32. The method according to claims 30 to 31, characterized in that the filter detects clusters of DNA binding sites using profiles or weightmatrices.
  - 33. The method according to claim 32, characterized in that the filter detects densities of clusters of DNA binding sites.
- 34. A method for identifying a MAR sequence characterized in that it comprises at least one filter detecting clusters of DNA binding sites using profiles or weightmatrices.
  - 35. A purified and isolated MAR DNA sequence identifiable according to claims 15 to 33 or claim 34.
- 50 36. The purified and isolated MAR DNA sequence of claim 35, containing at least 10% of dinucleotide TA on a stretch of 100 contiguous base pairs.

37. The purified and isolated MAR DNA sequence of claim 36, containing at least 33% of dinucleotide TA on a stretch of 100 contiguous base pairs.

- 38. The purified and isolated MAR DNA sequence of claims 35 to 37, further containing at least 12% of dinucleotide AT on a stretch of 100 contiguous base pairs.
  - 39. The purified and isolated MAR DNA sequence of claim 38, further containing at least 33% of dinucleotide AT on a stretch of 100 contiguous base pairs.
- 10 40. The purified and isolated MAR DNA sequence of any of claims 35 to 39, comprising a sequence selected from the sequences SEQ ID Nos 1 to 27, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- 15 41. The purified and isolated DNA sequence of claim 40, comprising a sequence selected from the sequences SEQ ID Nos 24 to 27, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- 20 42. The use of a purified and isolated DNA sequence comprising a first isolated matrix attachment region (MAR) nucleotide sequence which is a MAR nucleotide sequence selected from the group comprising:
  - a purified and isolated DNA sequence of claims 1 to 9,
  - a purified and isolated MAR DNA of claims 35 to 41,
  - the sequences SEQ ID Nos 1 to 27,

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- a purified and isolated cLysMAR element and/or fragment,
- a synthetic MAR sequence of claims 12 to 14,

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants for increasing protein production activity in a eukaryotic host cell.

- 43. The use of the purified and isolated DNA sequence of claim 42, characterized in that said purified and isolated DNA sequence further comprises a promoter operably linked to a gene of interest.
- 44. The use of the purified and isolated DNA sequence of claims 42 or 43, characterized in that said purified and isolated DNA sequence further comprises at least a second isolated matrix attachment region (MAR) nucleotide sequence which is a MAR nucleotide sequence selected from the group comprising:
  - a purified and isolated DNA sequence of claims 1 to 9.
  - a purified and isolated MAR DNA of claims 35 to 41,
  - the sequences SEQ ID Nos 1 to 27,
  - a purified and isolated cLysMAR element and/or fragment,
  - a synthetic MAR sequence of claims 12 to 14,
- a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants for increasing protein production activity in a eukaryotic host cell.
- 45. The use of the purified and isolated DNA sequence of claim 44, characterized in that said first and at least second MAR sequences are located at both the 5' and the 3' ends of the sequence containing the promoter and the gene of interest.

46. The use of the purified and isolated DNA sequence of claim 44, characterized in that said first and or at least second MAR sequences are located on a sequence distinct from the one containing the promoter and the gene of interest.

- 5 47. The use of the purified and isolated DNA sequence of any of claims 42 to 46, characterized in that said purified and isolated DNA sequence is in the form of a linear DNA sequence as vector.
- 48. A method for transfecting a eukaryotic host cell, said method comprising
  10 a) introducing into said eukaryotic host cell at least one purified DNA sequence
  comprising at least one DNA sequence of interest and/or at least one purified and
  isolated DNA sequence consisting of a MAR nucleotide sequence or other chromatin
  modifying elements,
- b) subjecting within a defined time said transfected eukaryotic host cell to at least one additional transfection step with at least one purified DNA sequence comprising at least one DNA sequence of interest and/or with at least one purified and isolated DNA sequence consisting of a MAR nucleotide sequence or other chromatin modifying elements
  - c) selecting said transfected eukaryotic host cell.

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- 49. The method of claim 48, characterized in that said DNA sequence of interest is a gene of interest coding for a protein operably linked to a promoter.
- 50. The method of claims 48 and 49, characterized in that the selected transfected eukaryotic host cells are high protein producer cells with a production rate of at least 10 pg per cell per day.
  - 51. The method of claims 48-50, characterized in that the MAR nucleotide sequence is selected from the group comprising:
    - a purified and isolated DNA sequence of claims 1 to 9.
    - a purified and isolated MAR DNA of claims 35 to 41.
    - the sequences SEQ ID Nos 1 to 27,
    - a purified and isolated cLysMAR element and/or fragment,
    - a synthetic MAR sequence of claims 12 to 14,
- a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
- 52. The method of claims 48-50, characterized in that the MAR nucleotide is a purified and isolated sequence according to claims 1 to 9, a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.
  - 53. The method of claims 48 to 52, characterized in that the defined time corresponds to intervals related to the cell division cycle.
  - 54. The method of claim 53, characterized in that the defined time is the moment the host cell just has entered into a second cell division cycle.
- 55. A method for transfecting a eukaryotic host cell, said method comprising cotransfecting into said eukaryotic host cell at least one first purified and isolated DNA sequence comprising at least one DNA sequence of interest, and a second and isolated purified DNA comprising at least one MAR nucleotide selected from the group comprising:

- a purified and isolated DNA sequence of claims 1 to 9,
- a purified and isolated MAR DNA of claims 35 to 41,
- the sequences SEQ ID Nos 1 to 27,
- a purified and isolated cLysMAR element and/or fragment,
- a synthetic MAR sequence of claims 12 to 14,

a sequence complementary thereof, a part thereof sharing at least 70% nucleotides in length, a molecular chimera thereof, a combination thereof and variants.

- 56. A process for the production of a protein wherein
- a) a eukaryotic host cell transfected according to claims 48 to 54 or claim 55, is cultured in a culture medium under conditions suitable for expression of said protein and
  - b) said protein is recovered.

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- 15 57. A eukaryotic host cell transfected according to any one of claims 48 to 54 or claim 55.
  - 58. A cell transfection mixture or kit comprising at least one purified and isolated DNA sequence according to claims 1 to 9, 10 to 11, 12 to 14 or 35 to 41.
- A transgenic organism characterized in that at least some of its cells have stably incorporated at least one DNA sequence of claims 1 to 9, 10 to 11, 12 to 14 or 35 to 41.
- 60. A transgenic organism characterized in that its genome has stably incorporated at least one DNA sequence of claims 1 to 9, 10 to 11, 12 to 14 or 35 to 41.
  - 61. The transgenic organism of claims 59 and 60 characterized in that some of its cells have been transfected according to the method of claims 48 to 54 or claim 55.
- 30 62. A computer readable medium characterized in that it comprises computerexecutable instructions for performing the method for identifying a MAR sequence of claims 15 to 33 and/or claim 34.

FIG.1

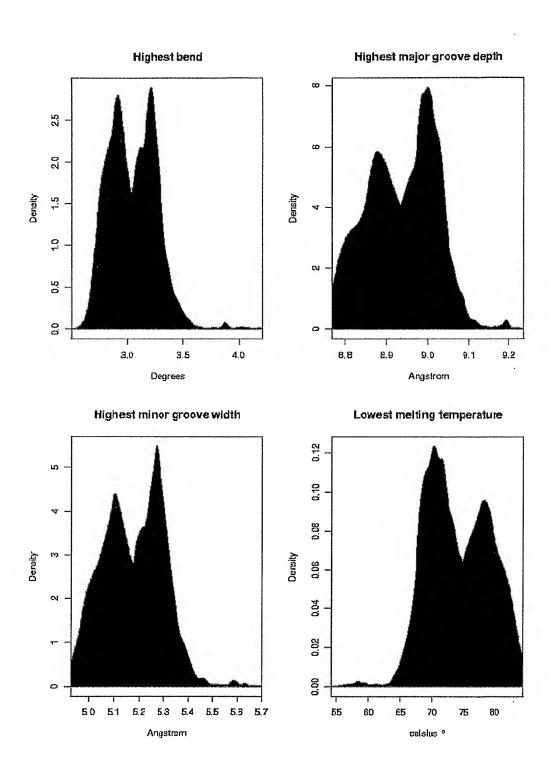


FIG.2

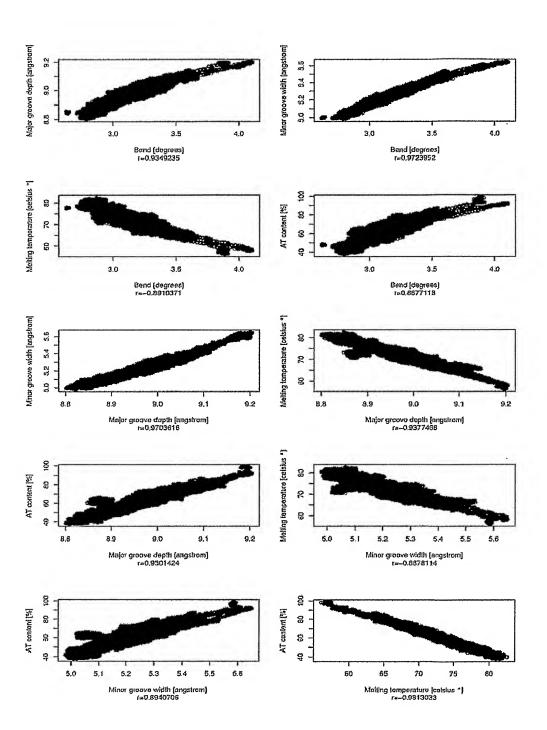


FIG.3

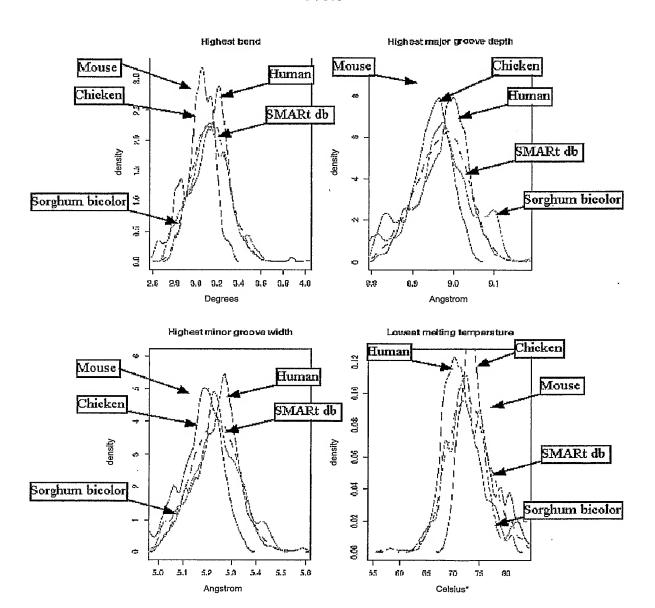


FIG.4

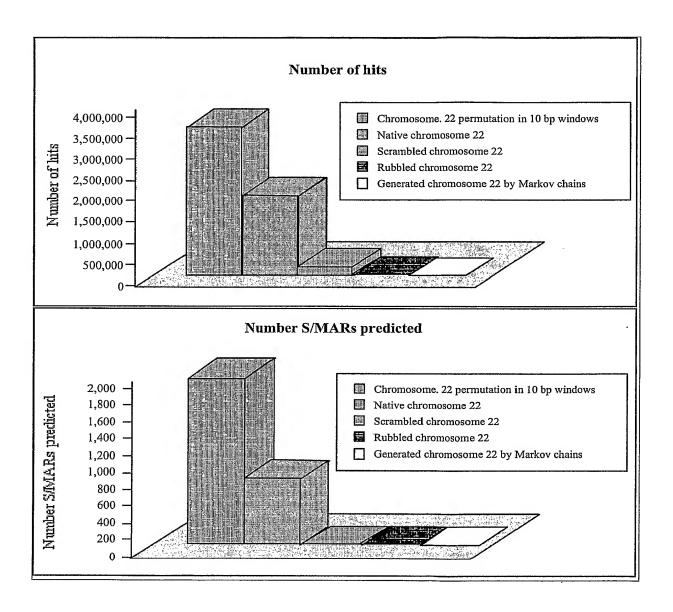


FIG.5

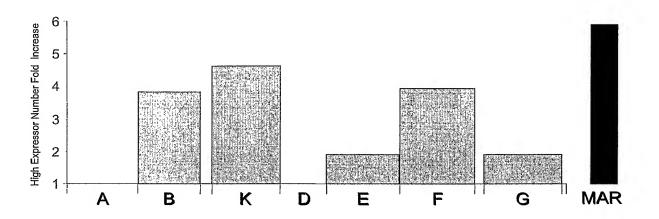


FIG.6

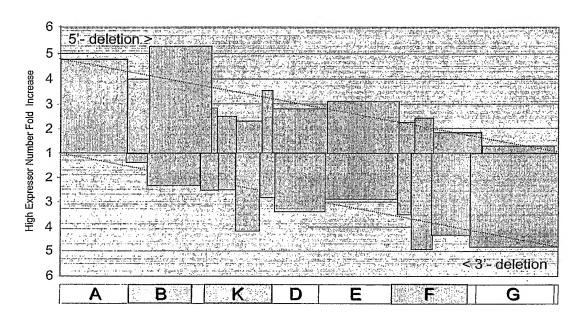


FIG.7

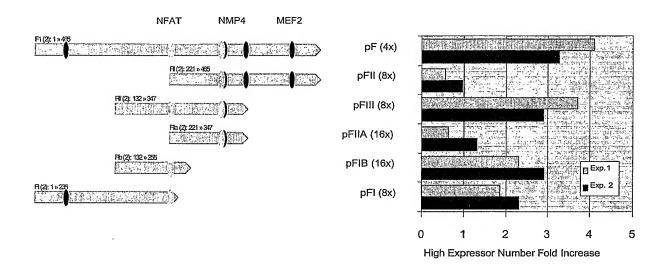
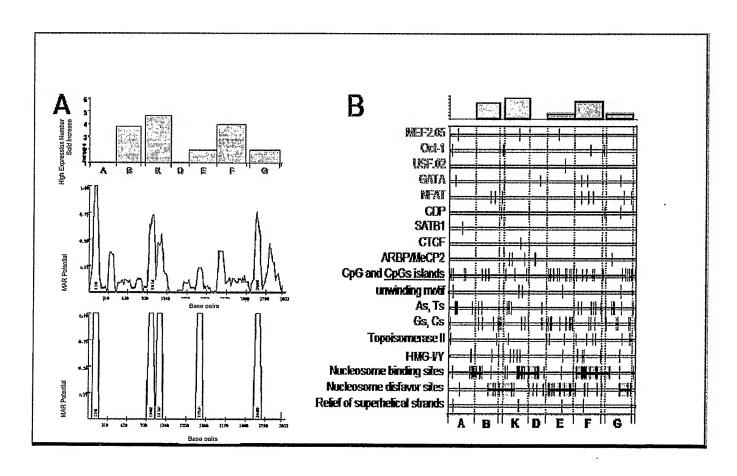


FIG.8



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FIG.9

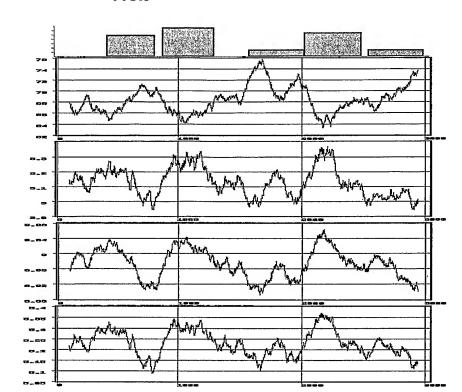
(A)

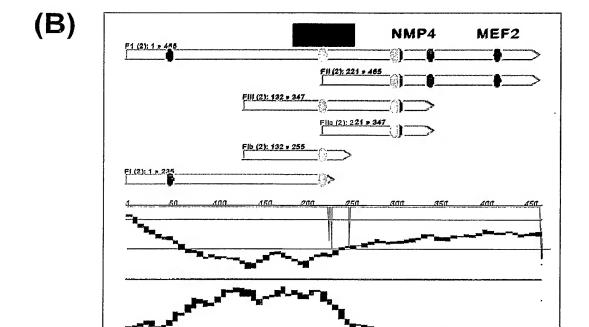
Melting temperature (°C)

Bend (degrees)

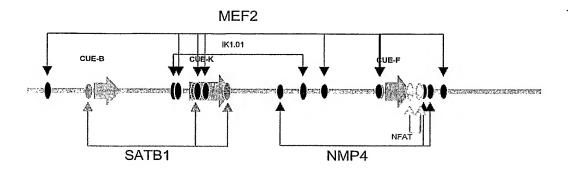
Major groove depth (Å)

Minor groove width (A)

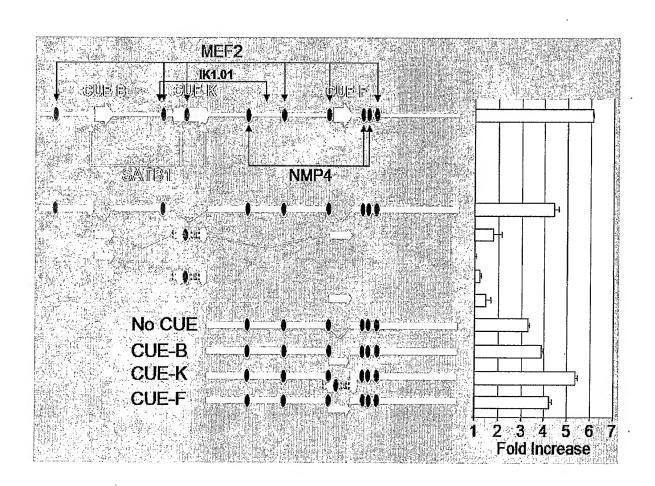




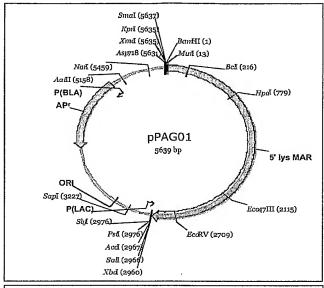
**FIG.10** 

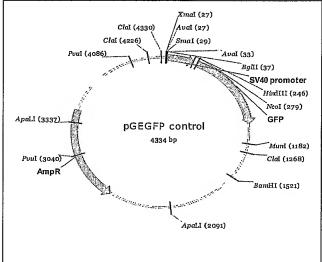


**FIG.11** 



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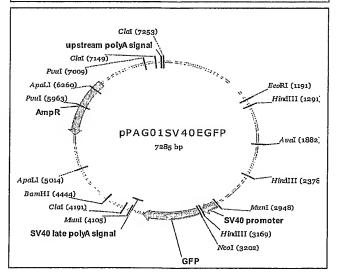


FIG.13

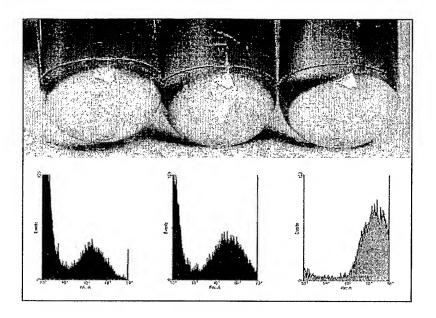
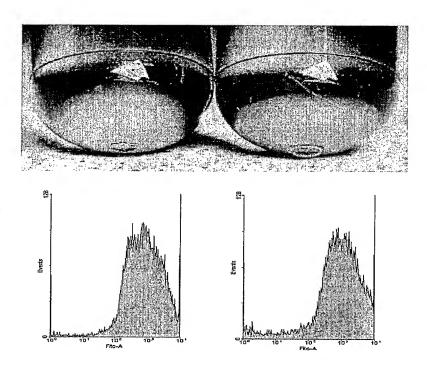
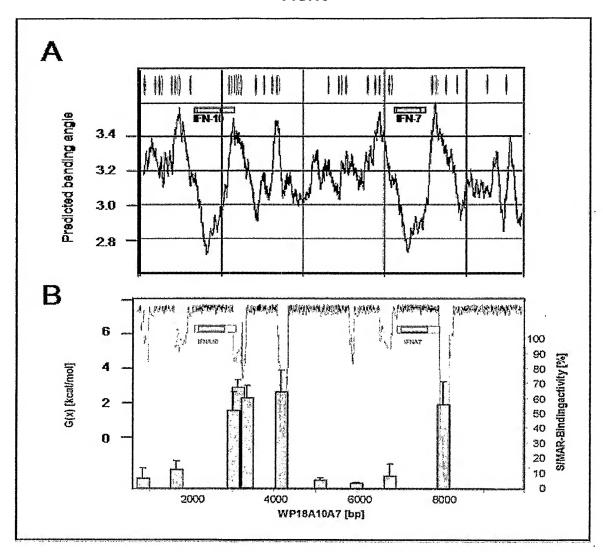


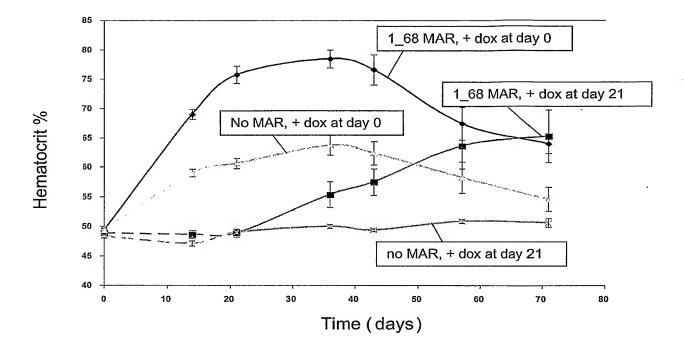
FIG.14



**FIG.15** 

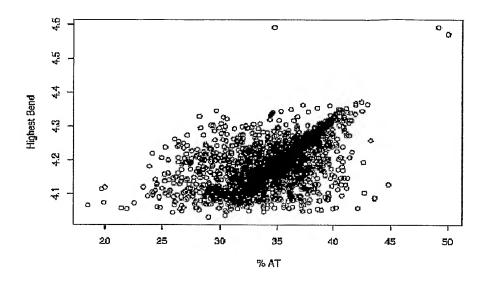


**FIG.16** 

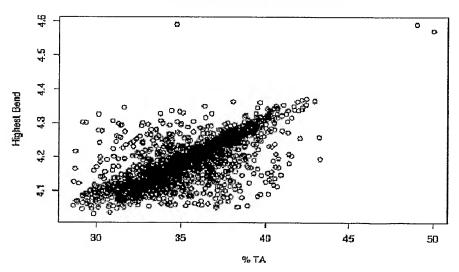


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FIG.17

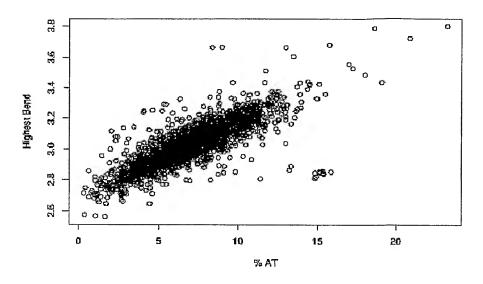






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FIG.18



% TA dinuclectide vs Bent DNA

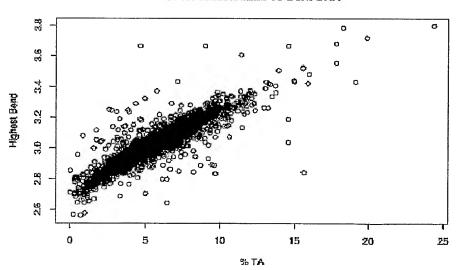
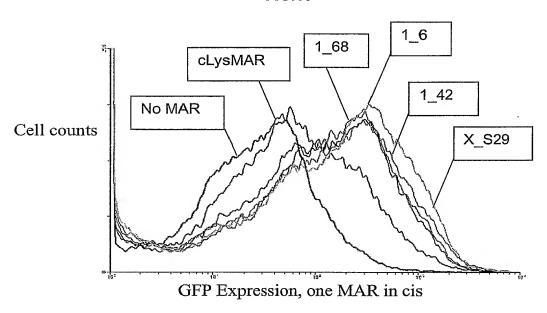
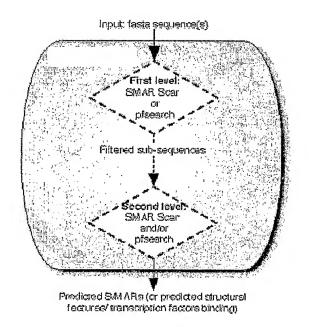


FIG.19



**FIG.20** 



## SEL PCT 012.ST25 SEQUENCE LISTING

<110> Selexis S.A.

## <120> HIGH EFFICIENCY GENE TRANSFER AND EXPRESSION IN MAMMALIAN CELLS BY A MULTIPLE TRANSFECTION PROCEDURE OF MAR SEQUENCES

<130> SEL PCT O12

<150> US 60/513,574

<151> 2003-10-24

<150> EP 04 002 722.9

<151> 2004-02-06

<160> 241

<170> Patentln version 3.1

<210> 1

<211> 320

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

### **SEL PCT 012.ST25**

<222> (1)..(320)

<223> MAR of human chromosome 1, nt from 36686 to 37008

<220>

<221> misc binding

<222> (1)..(320)

<223> MAR of human chromosome 1, genomic contig; 36686 to 37008

<210> 2

<211> 709

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(709)

<223> MAR of human chromosome 1, nt from 142276 to 142984

### **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(709)

<223> MAR of human chromosome 1, genomic contig; 142276 to 142984

<400> 2 tacaatatat tttctattat atatattttg tattatatat aatatacaat atattttcta 60 ttatatataa tatattttgt attatatata ttacaatata ttttgtatta tataatatat 120 aatacaatat ataatatatt gtattatata ttatataata caatatatta tatattgtat 180 tatatattat atataatact atataatata ttgtattata tattatatat aatactatat 240 aatatattt attatatat atatataata caatatataa tatattgtat tataatacaa 300 360 ttataatata taataataat ataatatat attatata attatata 420 480 tataatatat titigtattat atataatata tititattatg tattatagat aatatatitt 540 attatatatt atatataata caatatataa tatattttgt attgtatata atatataata 600 caatatataa tatattgtat tatatataat attaatatat tttgtattat atatttatat tttatattat aattatgttt tgcattatat atttcatatt atatatacc 709

<210> 3

<211> 409

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

### **SEL PCT 012.ST25**

<222> (1)..(409)

<223> MAR of human chromosome 1, nt from 1368659 to 1369067

<220>

<221> misc binding

<222> (1)..(409)

<223> MAR of human chromosome 1, genomic contig; 1368659 to 1369067

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attatgtata tatacataaa tacatatgca tatacattat gtatatatac ataaatacat 120
atgcatatac attatgtata tatacataaa tacatatgca tatacattat gtatatatac 180
ataaatacat atgcatatac attatgtata tatacataaa tacatatgca tatacattat 240
gtatatatac ataaatacat atgcatatat tatatacata aattatatta tatacataat 300
acatatacat atattatgtg tatatataca taaatacata tacatatatt atgtgtatat 360

409

atacatgata catatacata tattatgtat atatacat aaatacata

<210> 4

<211> 394

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(394)

<223> MAR of human chromosome 1, genomic contig; 2839089 to 2839482 Seite 4

### **SEL PCT 012.ST25**

<400> 4
tatgtatata tacacacata tgtatatata cacacatatg tatatacgta tatatgtata 60
tatacacaca tatgtatata cgtatatatg tatatataca cacatatgta tatacgtata 120
tatgtatata tacacacata tgtatatacg tatatatgta tatatacaca catatgtata 180
tatgtatata tacacacata tgtatatacg tatatatgta tatatacaca catgtgtata 240
tatatataca catatgtata tatgtatata tacacacata tgtatatatg tgtatatatg tgtatgtata 300
tatacacaca tatgtatata tacacatata tatgtatata tacacacata cttatatata 360
cacatatata tgtatatata cacatatgta taca
394

<210> 5

<211> 832

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(832)

<223> MAR of human chromosome 1, genomic contig; 1452269 to 1453100

<400> 5

#### **SEL PCT 012.ST25**

atacacaatg tatataacta tatatacaat atatattact atatatacta tatatattac 360 tatacatact atatattact ctatatatac aatatata ta ttacaatata tactacatat 420 tactacatat actttatata ttactatata tactatatat tactgtatat acaatatata 480 540 600 cacattatat atgactatat atacacacta tatatattac tatatataca caatatataa 660 actatatatt actatatata cacaatatat attactctat gtatacacta tatatattac 720 780 832 

<210> 6

<211> 350

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(350)

<223> MAR of human chromosome 1, genomic contig; 831495 to 831844

#### **SEL PCT 012.ST25**

<210> 7

<211> 386

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(386)

<223> MAR of human chromosome 1, genomic contig; 1447225 to 1447610

<400> 7

acatttaatt taattatata ctgctatata taattaaatc tatatatcta tataacttat 60
aatttattt aatttaatta tatatactat atagttatat atacatatat gtaattatat 120
atagtataat tatagtatat atgtatatat aatgtaagta aatatatagt atatatttat 180
atatactata tatttataca tatgtcttta tatatactaa tatatataca catatgtaat 240
atgtacatat ggcatatatt ttatagtgta tatatacata tatgtaatat atatagtaat 300
atgtaaatat atagtacata tttaattata tggtaatata tacacatata tgtaatatgt 360
gtattatagt acatatttta tagtat 386

<210> 8

<211> 585

<212> DNA

<213> Homo sapiens

<220>

### **SEL PCT 012.ST25**

<221> misc\_binding

<222> (1)..(585)

<223> MAR of human chromosome 1, genomic contig; 4955365 to 4955949

<400> 8 60 atacacacat atacacatat gtacgtatat atactatata tacacacata tacacatatg 120 tacgtatata tactatatat acacacatat acacatatgt acgtatatat actatatata 180 gtatatatac tatataca cacatataca catatgtacg tatatattat atatacacac 240 300 atatacacat atgtacgtat atatactata tatacacaca tatacacata tgtacgtata tatactatat atacacacat atacacatat gtacgtatat atactatata tacacacata 360 420 tacacatatg tacgtatata tactatatat acacacatat acacatatgt acgtatatat actatatata cacacatata cacatatgta cgtatatata ctatatatac acacatatac 480 acatatgtac gtatatatac tatatataca cacatataca catatgtacg tatatatact 540 585 atatataccc atacacatac gtatatacgt acatatatat acgta

<210> 9

<211> 772

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(772)

<223> MAR of human chromosome 1, genomic contig; 5971862 to 5972633

# **SEL PCT 012.ST25**

<400> 9 agtaaacata tatatagtaa atatatatag tgtatatata gtaaatatat atagtgcata 60 tatatagtgc atatatatag totatatata gtaaatatat agtgtatata tatagtaaat 120 atatatagtg tatatatagt aaatatatat agtaaatata tatatactat atatagtaaa 180 240 300 360 tatatagtat atatatagta aatatatata tagtatatat atagtaaata tatatagtat 420 atatatagta aatatatata gtatatatat agtaaatata tatagtatat atatagtaaa 480 tatatataca cigitatata atagtaaata tatatacaci giatatatat agtaaatata 540 tatacactgt atatatatag taaatatata tacactgtat atatatagta aatatatata 600 cactgtatat acatagtaaa tatatataca ctgtatatac atagtaaata tatatacact 660 gtatatacat agtaaatata tatacactgt atatacatag taaatatata tacagtgtat 720 atacatagta aatatatata cagtgtatat acatagtaaa tatatataca gt 772

<210> 10

<211> 304

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(304)

<223> MAR of human chromosome 1, genomic contig; 6221897 to 6222200

<400> 10

# **SEL PCT 012.ST25**

<210> 11

<211> 311

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(311)

<223> MAR of human chromosome 1, genomic contig; 9418531 to 9418841

<400> 11

tataatttat a

311

<210> 12

<211> 302

# **SEL PCT 012.ST25**

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(302)

<223> MAR of human chromosome 1, genomic contig; 15O88789 to 15089090

at 302.

<210> 13

<211> 461

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(461)

<223> MAR of human chromosome 1, genomic contig; 6791827 to 6792287

# **SEL PCT 012.ST25**

tatataatat atattatata tacacatata taatatatat	60
atatattata tatacacata tataatatat attatatata	120
tatatacaca tatataatat atattatata tacacatata taatatatat	180
catatataat atatattata tatacacata tataatatat attatatata	240
atatatatta tatatacaca tatgtaatat atattataca cacacatata atatatatta	300

aatatataca catatataat atatatata tatatgcaca t 461

<210> 14

<100> 13

<211> 572

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(572)

<223> MAR of human chromosome 1, genomic contig; 163530 to 164101

<400> 14

# **SEL PCT 012.ST25**

<210> 15

<211> 357

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(357)

<223> MAR of human chromosome 1, genomic contig; 1842332 to 1842688

<400> 15

<210> 16

<211> 399

<212> DNA

# **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(399)

<223> MAR of human chromosome 1, genomic contig; 2309560 to 2309958

<400> 16

<210> 17

<211> 394

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(394)

<223> MAR of human chromosome 1, genomic contig; 2231759 to 2232152

# **SEL PCT 012.ST25**

<400> 17

atatatactt ataaattata tacttatata tacttataaa ttatatactt atatatactt ataaattata 120 tacttatata tacttataaa ttatatactt ataaattata tacttatata 180 tacttataaa ttatatactt ataaattata tacttataaa 140 tacttataaa ttatatactt ataaattata tacttatata 240 ttatatactt atatataatt ataaattata tacttataaa ttatatactt 300 atatataatt ataaattata tacatatata taattataaa ttatatacat ataaattata 360 aaattatata catatataat tataaattat ataa

<210> 18

<211> 387

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(387)

<223> MAR of human chromosome 1, genomic contig; 7406524 to 7406910

<400> 18

# **SEL PCT 012.ST25**

acataatata ttatatata tatatta

387

<210> 19

<211> 370

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(370)

<223> MAR of human chromosome 1, genomic contig; 9399572 to 9399941

<400> 19

tatacacata tgtatacaca tatatacaca tatatacaca catatataca catatataca 120

cacatatata cacatatata cacatatata cacatataca catatataca catatataca 180

tatatacaca tatatataat atacacacat atatatacac atatatacac acatatatac 240

acatatatac acatatatac atatatacac atatatacat atatacacac atatatacac 360

atacatatac

370

<210> 20

<211> 377

<212> DNA

<213> Homo sapiens

<220>

# **SEL PCT 012.ST25**

<221> misc binding

<222> (1)..(377)

<223> MAR of human chromosome 1, genomic contig; 12417411 to 12417787

<400> 20

<210> 21

<211> 1524

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1524)

<223> MAR of human chromosome 1, genomic contig; 1643307 to 1644830

<400> 21

tataaatata tataaatata taaatatata taaatatata aatatatata aatatatata 60 aatatataaa aatatataaa tatatataaa tatataaaa tatataaaa tatataaaa tatataaaa cataaaaata 120

# **SEL PCT 012.ST25**

tatataaata tatataaata tataaaaata tataaatata taaatatata aaaatataca 180 aatatataaa tatatacata aatatatata aatatata aatatataaa aatatatata 240 aatatataaa tatatataaa tatatataaa tatatataaa tatataaaaa tatatataaa 300 tatataaata tataaaaata tataaaata tataaatata taaatatata taaatatata 360 aatatataaa taaatataag tatttatgaa tatatatgaa tatataaata tataaaaaat 420 atatataaat atataaatat atataaatat ataaatatat acatatatac atatataaat 480 540 aatatataaa tatatataaa tataaatata taaaaatata taaaaatata tataaatata 600 taaatatata taaatatata aatatatata aatatataa aatatataaa tatataaa 660 tatatataaa tatataaata tataaatata tataaatata tataaatata taaatatata 720 aatataaata tataaatata tataaatata tataaatata taaatatata taaatatata 780 taaatatata taaatatata taaatatata aatatata aatatata taaatatata 840 taaatatata aatatataaa tatataaaaa tatataacaa tatataaata tatataaaaa 900 tatataacaa tatataaata taaatatata taaaaatata taacaatata taaatataaa 960 tatatataaa tatataaata taaatataaa aaatatatat aaatatataa atatatataa 1020 atatataaat gtataaatat atataaaaat atataacaat atataaatat ataaatata 1080 aacaatatat aaatatataa aaatatataa caatatataa atataaatat atataaaaat 1140 tatataaata tataaatata tatataaata tatataaata tataaatgta taaatatata 1260 taaatatata aatatataaa aatatataaa tatatataaa tatatataaa tatataaa tatataaata 1320 taaatatata aatatata aatatataaa tataaatata taaacatata taaatatata 1380 taaataaaca tatataaaga tatataaaga tataaagata tataaatata taaatatata aagatatata aatatataaa gatatataaa tatataaaga tatataaata tataaagata 1500 tataaatata atatataaat atat 1524

# **SEL PCT 012.ST25**

<211> 664

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(664)

<223> MAR of human chromosome 1, genomic contig; 1398763 to 1399426

<400> 22

60 120 180 240 300 tacacacata tatataaaat atatatatac acacatatat aaaatatata tatacacaca 360 tatataaaat atatatatac acatatatat aaaatatata tatacacata tatataaaat 420 480 540 atataaaata tatatacaca catatatata aagtatatat atacacacat atatataaaa 600 caca 664

<210> 23

<211> 1428

<212> DNA

#### **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1428)

<223> MAR of human chromosome 2, genomic contig; 17840365 to 17841792

<400> 23

60 120 180 atattagata taatatata ctaatatata tatatttat atatataata tatctctaat atatatattt tatatgtata taatatatct ctaatatata tatattttat atgtatataa 240 tatatctcta atatatat tttttatata taatatatct ctaatatata tattttatat 300 atataatata tatctaatat atataatata tatattagat atatataaaa tatatagat 360 attatataca atatatatta tatatatttt atatacatta tatattatat atattttata 480 tacaatatat attatatatt ttatatacaa tatatattat atatattta tattttata 540 600 660 ataaattata atattitta tatatataat atgtattita tatataatat attataatat 720 atattttata tataatatat tataatatat attttatata taatatatta taatatatat 780 900 

#### **SEL PCT 012.ST25**

<210> 24

<211> 4624

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(4624)

<223> MAR 1 6 of chromosome 1

<400> 24

ggatcttaaa tctattttat ttattattt tteatgtggc caataccctc caccccttc 60

ttetgtetet tteaacttat tgtggttace ttgaggetac etgagacagt aggettgggt 120

ggggaagtat gcattetaag tgtaaagttt gatgagettt gacaaatgte aacccatgta 180

ccagaacatt tteatcacce ataaaatete cettgtgtea ettgecagte agtgtetatt 240

ctagtateea actcetgget ccaagaaace attgaactgt tttetgteac tataaattag 300

atttgtettt tetagagttt catgtaaatg gaatcataca etaagtacte tttgtgeetg 360

gettetgete agcataatgt ttttgagaat cattcatget getgeatgtt tteagtagtt 420

### **SEL PCT 012.ST25**

cattttttta aataggtgaa ttgtaactca ttctgtgaat ataccatatt ctgtcttcca 480 tttatctgtt agtggatett taggtegttt etagttttgg getattgeaa ataaagetge 540 tgtaaatatt aatgcacaag ttttccatgt tcatatgttt catttcactt aggaaaatac 600 ctaagagagg aattgcacat attaaaaaaa ttttaaaaaac tactaagctg ttctccaaaa 660 tggttgtaca atttttattc ccaagagcaa tatgagtgtt taattgctcc acattctcac caacacttoo tocttottag ttttattttc attotttca ttgttatgtc tgtgaggcag cattgatgtg catgtctctg agtgtcatct tagcggtgat gctgagcatc agttcacgtc 840 cttataggcc gtttgtatat ctgctttgtg aaatgtctgt tcaaatcttt tgcctatttt 900 aaattgagtt gtgttcgtct tcttaggatt aagtaatgag ttaaaaatat ttctgataca 960 aatctttcat tatatatttc taatgctttc tcatctatag tttattttct catattcttt 1020 aactgtatct tttgaagage aaattttact tttgattatg cecaatttat caagttttta 1080 tatggetett ttgattatge ecataateae attagaettt geetaaceea agtttgeaga 1140 gattttttct tttatgcttt tatctagaaa ttttgtagtt ttaggtttta aaaaagttta 1200 atttatttat ttgagacagg gtattgctct ttacatatac tggagtgcag tgatgcaatc 1260 atggctcact gcagcctcaa cctcttgggc tcaagcggtt ctcccatctc agagtcctga 1320 gtagctggcc aggtgcatgc cagcttcaat gtgtttttca tttgcatttc cctgataatt 1380 attgacgttg agcattttt tcatatatca gttagctatt tgtacgtctt cttttgagaa 1440 acatetatte gggtettttg eccattttaa agteagatgg tttgtttgte agetattgag 1500 tigitigagi teetigiata tietggatat taccatetig teagatgeae agittigeaaa 1560 ttttttttt ctattttgta ggttgtctct ttctctgttg tttcctccgg tatgcagaag 1620 ttttttagtg tgatgtaatt tcatttgtct gtttttgctt ttgttgcctg tactttctta 1680 ttcttatcca aaaaatcttt atctagatca atgtcacgaa gagtttctcc tctgttttct 1740 tcgagtagtt ttttataatt ttgggtatac atttaagtct ttaatctatt tggaattgat 1800 ttttgcatat ggtgagagat cagagtctaa tttcatactt ttggatgtgg aaagctagtt 1860 ttttcagcac catttattga agagactgtc tcttctccaa tgtgtgttct ttgtgccttc 1920

# **SEL PCT 012.ST25**

gtcaaaaatc agttggctgt gcgtggattt atttctgtgt tctctatttt gttccattgg 1980 tctagtttta gccttaaatt taggtctgca atttttttt ttttgtatat ggtgtgaagt 2040 aagagtcaaa gttcattatt tttcatatgg atatgtaatt actccagtac catcatttag 2100 tttgaatgga ctgtcctttc tccatggaat tacatgggca tcttttgtct gaaaccaatt 2160 atgtatgttt acgtatgtgt atgtttatgc atatgttata ggtttaatat atattaatat 2220 acctataaca tatgcatata cttatttata tataacatgc atgtacttat ttatatatac 2460 aatatatat tatatattat ataatatat atatgtatt atatattata tatcatatat 2520 tatatgtatt tatatattat atatcatata atatatatat ttatattata tatattatat 2580 gatatataat attatataat gtattaatat atattaaacc tatatttata attctggact 2640 cactattttg tttcattggt gtctgtgtgt atctaaccct atgccaataa tgtactatct 2700 taattaccat agetttatag taagetttga aatcagatag tgtatttttt atcattgttt 2760 tttaaaataa tagtttatct ttttatttga atttgtaatc agctagtcag tttctgcaaa 2820 agettactg ggattttgct tggaattatg ttacatctgt agcatgtact atccaatatt 2880 ttaaaattaa aacttaataa ttggtteete atteacacta ceatatgtea agtgtteaat 3000 agccacatat ggtcaatgtc ttggaaaagt caatacagta catttccatt attgcagtaa 3060 gttetgteaa acageactat egtagaeega ttaggagaga aetgaettaa eagtattgga 3120 tgctccagtc aatgaacatc ttttttttt tcatttattt cagtagtctc tgcagtatat 3180 tatagatttc agtttacata ttttgcatat attttattaa atgtataacg gtagaagtac 3240 tattattgga tgatgtgttc tatagatgta ttttaggtca agtttgttga tagtgttgtt 3300 taaatctcgt atacctcttg attitttat ttacttgttc tttgaattac tgagacagga 3360 atgitatate ettaaetata titigigaatt tatteaette tieetteagt tetgitaaet 3420

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tttgcttagg tgctttttaa aaatgaaact ttcaatctct gccttttaat tgtagcattt 3480 agaccattta cattcaatgt aattatcaat atcagtttat ttaagtctga agttgtgcaa 3540 tttttcctct acctatatta taaatctttc tatatacaaa acacatgcta tgttttctgc 3600 atatgtttta aatgacaccc ggaaagcatt gacactattt ttgctttagg ttatctttca 3660 aagatgttaa aaatgagaaa gaaatattet geatttatee atacaettat tatttgeaaa 3720 ggttttttta aatacettig tgtagattic agttaccaac ttgtatticc ttcagettga 3780 agaacttaca attictigta ggacaggict ctgacaacaa attatctcag ctittcttig 3840 tctaaaaaag ttattgcctt tatttttaaa atatattttc actggatatt gaattttagg 3900 tgataatctt tttttttttg ttagcacttt aaatatgtct tctaatgtcc tcttgctttc 3960 atagtttctg atgagaagtc tactgttatt agtatctctt tgtgtgtgtc tctctttttt 4020 ccctctctgc tattatggct attittttt ttttttttt ttttggtcac tggtgtcage 4080 tgtgtgtgtg tagctgatgt tctttgagct ttagaatctg tgagtttgta gttttcatca 4200 attattttt cttttcattc cttttattta ctcatgttcg tgttttattt tatattttta 4260 agaattttgt gcgtatttgt aataactgtt taaatgtcat ttgtgaattc cattgcttct 4320 aggtaggatt ctattgacag atattttttc cctgacgaga ggtcatactt tccttattct 4380 tcatgtatct agtggttttt ggttgaatac tggatatttt gaattttatg ggagtgctga 4440 attetacaat atteettaaa aatgtgttgg attttgtttt ageagatage tatettaett 4500 gaagatcaat ttcatatttt ttgatgttca ttttttcatt tattaaagaa taggtccatg 4560 gtagagttta ctgatatcaa cetttetggt gtetetaata aatgeaacat atteaataag 4620 atcc 4624

<210> 25

<211> 3616

<212> DNA

<213> Homo sapiens

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<220>

<221> misc\_binding

<222> (1)..(3616)

<223> MAR 1 68 of chromosome 1

<400> 25 60 gactotagat tataccaacc toataaaata agagoatata taaaagoaaa tootottato 120 ttgcagatcc ctgaactgag gaggcaagat cagtttggca gttgaagcag ctggaatctg caattcagag aatctaagaa aagacaaccc tgaagagaga gacccagaaa cctagcagga 180 gtttctccaa acattcaagg ctgagggata aatgttacat gcacagggtg agcctccaga ggettgteea ttageaactg etacagttte attateteag ggateacaga ttgtgetace tattgcctac catctgaaaa cagttgcttc ctatatttca tccagtttaa tatttattta aaccaagaag gttaatctgg caccagctat tccgttgtga gtggatgtga aagtaccaat tecattetgt tttactatta actateettt geettaatat gtateagtag gtggettgtt 480 gctaggaaat attaaatgaa tggcatgttt cataggttgt gtttaaagtt gttttttgag 540 600 ttaaatetti ettaataat aettietgat gicaaaaaca ettagaagte atggtgttga acatetatat agggttggat etaaaatage ttettaacet tteetaacea etgtttttgt 660 ttgtttgttt ttaactaagc atccagtttg ggaaattctg aattagggga atcataaaag 720 gtttcatttt agctgggcca cataaggaaa gtaagatatc aaattgtaaa aatcgttaag 780 aacttetate ceatetgaag tgtgggttag gtgeetette tetgtgetee ettaaeatee 840 tattttatct gtatatatat atattcttcc aaatatccat gcatgggaaa aaaaatctga 900 tcataaaaat attttaggct gggagtggtg gctcacgcct gtaatcccag cactttggga ggctgaggtg ggcggatcat gaggtcaaga gatcgagacc atcctgacca atatggtgaa 1020 accecatete tactaaagat acaaaactat tagetggacg tggtggcacg tgcctgtagt 1080

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# **SEL PCT 012.ST25**

atatcattct tatgccatgt tataaccagt ttgagagtgt tccctctgtt attgcattta 2640 agtttcagcc tcacacagaa attcagcagc caatttctaa gccctaagca taaaatctgg 2700 ggtgggggg ggggatggcc tgaagagcag cattatgaat agcaccatta taattaatga 2760 teteteagga agatttacaa teacaggtag cagataaaac aaatagtact gettetgeac 2820 ttcccctcct tttattcgct atgaaatttt atgggaaatc agtccagtga aaaatgtaag 2880 ctettaatet tteecagaaa teetaeetea tttgatgaat aetttgaggg aatgaattag 2940 agcatttttt tettttatag tetaettege atttaegaag tgaggaeggt agettagget 3000 gcctggccaa ctgatgagaa ggtcagaggc atttttagag acctctgttg tctttcattc 3060 atgttcattt tccacaaggc aagtaatttc caacaaatca gtgtcttcat tagtaataag 3120 attattaaca acaataatag tcatagtaac tattcagtga gagtccatta tatatcaggc 3180 attetacaag gtactttata tacatetgag taaaceteac acaattetac agggaggtat 3240 ttctatcccc atttaacaaa taaggaaacg aagtccaagt aaattaactt gcccaaggtc 3300 acacagatag tacetggcag aacaggaatt taaacetaaa tttgtccaac tecaaaagca 3360 geettetatt tgttataaat getgeetete attateacat attttattat taacaacaac 3420 aaacatacca attagcttaa gatacaatac aaccagataa tcatgatgac aacagtaatt 3480 gttatactat tataataaaa tagatgtttt gtatgttact ataatcttga atttgaatag 3540 aaatttgcat ttctgaaagc atgttcctgt catctaatat gattctgtat ctattaaaat 3600 3616 agtactacat ctagag

<210> 26

<211> 4660

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

#### **SEL PCT 012.ST25**

<222> (1)..(4660)

<223> MAR 1 42 of chromosome 1

<400> 26 60 gatcccttga ggtcagtagt ttaagaccag cctgaccaac atggtgaaac ccatctctac 120 taaaaataca aaaattagcc aggcgtggtg gcgggggcct gtaaccccag ctactcagga ggctgaggca caagaatctc ttgaacccgg gaggcggagg ttgcagtgag ctgagattgt 180 240 aaaaaaggcc gggcgcggtg gctgacgcct gtaatcccag cactttggga ggccgaggcg 300 ggtggatcat gaggtcagga gatcgagacc acagtgaaac cccgtctcaa ctaaaaatac 360 aaaaaattag ccgggcgcgg tggtgggcgc ttgtagtccc agctactcag gaggctgagg 420 caggagaatg gcgtgaacct gggaggcgga gcttgcagtg agccgagatg gcaccactgc 480 actocagoot gggcgaaaga gtgagactoo gtotcaaaaa aaaaaaaaaa ttagotgggt 540 atggtggtgc gtgcctgtaa tcccagctac tcgggaggct gaggcaggag aatcccttga 600 acctgggagg cggaggttgc agtgatctgc catcctgtca ctgcatcact acactccagc 660 720 tggtatgcac cagctgtagt cccagctact tgggaggctg agttgggggg attgcctgag 780 ccagggaggt cgaggettea gggagecatg attatgecae tgeaeteeag cetgggecae 840 agagtgaaac ettetgteaa aaacaaaaaa acaaaaaaac acagtgtgtt agatettget 900 agacttggtg atataattaa gaggccatta tgggcagaac tgtgccccct tccaaaattc atatataaat atatataaat atataaaat atataaatat atataaatat ataaatatat 1020 ataaatatat aaatatata aaatatataa atatatata atatataa atatataaa 1080 atatataaat atatataaat atataaaat atataaaaac ataaaaatat atataaatat 1140 atataaatat ataaaaatat ataaatatat aaatatataa aaatatacaa atatataaat 1200 atatacataa atatatataa atatataa atatataaaa atatatata atatataaat 1260

#### **SEL PCT 012.ST25**

atatataaat atatataaat atataaaat atataaaaat atatataaat atataaatat 1320 ataaaaatat atataaatat ataaatatat aaatatata aaatatataa atatataaat 1380 aaatataagt atttatgaat atatatgaat atataaatat ataaaaaata tatataaata 1440 atatataaat ataaatatat aaaaatatat aaaaatatat ataaatatat aaatatatat 1620 aaatatataa atatatataa atatataaa atatataaat atatataaat atatataaat atataaatat ataaatatat ataaatatat ataaatatat aaatatataa atataaatat 1740 ataaatatat ataaatatat ataaatatat aaatatata aaatatata aaatatatat 1800 aaatatatat aaatatataa atatatataa atatatatat aaatatata aaatatataa 1860 atatataaat atataaaaat atataacaat atataaatat atataaaaat atataacaat 1920 atataaatat aaatatatat aaaaatatat aacaatatat aaatataaat atatataaat 1980 atataaatat aaatataaaa aatatatata aatatataaa tatataaaa tatataaatg 2040 tataaatata tataaaaata tataacaata tataaatata taaatatata acaatatata 2100 aatatataaa aatatataac aatatataaa tataaatata tataaaaata tataacaata 2160 atatataaaa atatataaat atatataaat atataaaat atataaatat aaatatataa 2340 atataaagat atataaagat ataaagatat ataaatatat aaatatataa agatatataa 2460 atatataaag atatataaat atataaagat atataaatat ataaagatat ataaatataa 2520 tatataaata tataaagata tataaatata atataaaaat atataaatat atattaaaaa 2580 tatatacata taaatatatg tatattttt tgagatgggg tctcgctcag ccacccacgc 2640 tggagtgcag tggcacgage teggetcact gcaaccactg tetetegggt ccaagcaatt 2700 ctgtctcagc ctcccaagta gctgggatta caggcacctg ccatcatgcc cggctaattt 2760

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ttgtatttta gtagagatgg agtttcacca tgttggccag gttggtctcg aattcctgac 2820 ctcaggtgat ctgccggcct cggcctccca gtgctgggat tacaggcatg agtcaccacg 2880 cccggccta tatatattt tgagacaagc tctgtgtctc ccaggctgga gtgcagcagc 2940 atgateatga etcaetgtag eetagaeete eagggeteaa gtgattetee eaceteagee 3000 tgttttggag acagaatete tetetgteae eeaggetgga gtgeagtggt gtgateteag 3120 ctcagtgcaa cctccacctc ctgggttcaa gtgattctca tgcctcagcc tcctgagtag 3180 ctgggactac aggcgtgagc caccacgccc tgataaattt tgtattttt ttttcagatg 3240 gagtctcact ctgtcatact caggctggag tgcagtggcg tgattttggt ttattgcaac 3300 ctetgettee tgggtteaag egatteteet geeteageet eeagagtage tgggattaca 3360 ggcgcctgcc accatgccca cctagctaac ttttttttt tttttttga gatagagtct 3420 cactctgtca cccaggctgg agtgcaatgg ggcgatattg gctcactaca acctccacct 3480 cccaggttca agcgattctc ctgcctcagc ctcctgagta gctgggatta caggtgggtg 3540 ccaccacgcc agactaatat ttgtattatt agtagagacg gggtttcacc acattggtca 3600 3660 ggctggtttc gaactcetgg ceteaggtga tetgeetgee teggeeteec aaagtgetgg 3720 gattacagge atgagecact geggetggee caatttttge attttttgg tagagaeggg ggtttcacta tgcttcccag gctggtctca aactcctgga ctcaagcgat ctgcctgtct 3780 cagectecca aagtgeaggg attacagtea tgagecacca etgeaeggee ecaaaattta 3840 tttattttat tattattatt attttttaga tggagtctcc ttctgttgcc agattggaat 3900 geagtgeeae gateteaget eaetgeaace teeceeteet gggateaagt gattettttt 3960 tatacacgaa ttttgggcca ggcacagtgg cttatgcctg taatcccagc actttgggag 4080 ggccgaggtg ggtggatcac aaggtcagga gtttgagacc agcctggcca atatggtgaa 4140 accetgtete taetaaaaaa taeaaaaatt agetgggegt ggtggeacga geetgtaate 4200 ctggctactc tggaggctaa ggcaggagaa tcgcttgaac cggggaggca gaggttgcag 4260

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tgagccagga tcgcatcact gcactccagc ctgggtaaca gagcaagact ctgtctcaaa 4320 aaacaaacaa aacaaaacaa aacaaaataa ataacggtgc aaaattgaat atgccttttt 4380 gactctctaa atgcctcaga tccatttacc ctggggattt gtcctttcta gccccaccac 4440 catctcccct ctggaagact gctgacctat aaggataaag accagactct tgagcaggca 4500 cttagggtct tcctgcccat ccctatcccc aactccccct cagtaatttt ggctactagt 4560 atttctccac atctgaggct atcgtgggtc tcccttcagt ggtcatgaag gacaaggttg 4620 gagaagtttg ccctcgtgag tctgatgagg gattgggtgg 4660

<210> 27

<211> 3354

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(3354)

<223> MAR X\_S29 of chromosome X

<400> 27

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ctaaggcaaa aagctgaggt ttcaggagct tgaaggtaaa gaggaagaaa gaaatgggaa 180
tgggaattgg aaagacaaat atcgttaaga gaaaattgct tttaggagag gggaaagaat 240
ctatgtgtac ttaagactat ggaatcaatc ccatttaagc tgggaaacta gtttcatata 300
taactaataa attttattta cagaatatct atttacctga tctaggcttc aagccaaagg 360
gactgtgtga aaaaccatca gttctgtcat attcctaaaa aaaaattaaa aagttaaaaa 420

# **SEL PCT 012.ST25**

taaataaata ataaaacttc ttttctttca aaataatcaa ggtgcttatt cacatccatt ccaatttggg gaaatactta ttttcctatg attagcgaag agaaaagtaa cttgcatttc 540 600 aattcaagtt gatacatgtc acttttaaga ggtcaactaa tatttgctag ttgagctaac catatagget ttaaataett teatagtaga aagaaaatga aaateattag tgaactgtat 660 aaaatagate atactititg aaagaateag actgaagtit eegaaaaaaa gaagtaaget 720 tcaatgaaaa ggtaagtgaa tttagcattt actcagcatc tactatggac ttaacaccta 780 acagtagata atctgaaggc aaacatattt gtatagggac tgcagaatga tagatgataa 840 atatcatctc ttctatttga atgaatattt tttcaaatct ttcacacaca gtggtttgct 900 atggaaagat ttgtagtaca ttaaacaaat ctgaagatgg agttagaaag cttaggctat 960 gttttgagca caacatataa tttctctgtg attgtttctt catctttcaa atgaggttac 1020 tgtgaagatt aaatgagata actaaatgat gataaaataa tgtaatctta gcagcacctt 1080 atttaatctg tgcaacaact ctgtgaagtg agtagggctc agcttcagtc acttctctgc 1140 catttattaa ctaagatagt ttggaaagtt acccatctct tcagctgtaa aatgatgagg 1200 atcataccta ttttatgggg ctgcttttag gtacaaatat acaggcaagc actttgttaa 1260 tactaaagca ttacaccaat tagttttact cttttccatt cacacatgaa attaatgtaa 1320 teagaattet gtagattace taaatettet gttaacaegt gatatgeagt teaggttaaa 1380 tgtcagttga gttaccaaag cacatacata ctcaccaccc tatccaaatc tacaagcctc 1440 ccagtttgtc ttcactattt tggttaaatt aatatgaatt cctagatgaa aatttcactg 1500 atccaaatga aataaaaaat atattacaaa actcacacct gtaatctcaa cattttggga 1560 ggccaaggca ggtagatcac ttgaggccag gagttcaaga ccagcctgat caacatggtg 1620 aaaccctgtc tetactaaaa atacaaaaat tagccaggtg tggtggcatg tgcctgtagt 1680 cetacetact egggaggetg aggeacaaga ategettgaa tgtgggaggt ggaggttgea 1740 gtgacetgag ategtgecae tgeacteeag eetaggeaac agagtgagat eatgtgteat 1800 atacacatat atatacgtat atatatatat gtatatatat acatatatat acatatatat 1920

# **SEL PCT 012.ST25**

atatacgtat atatatacgt atatatatat caatgtaaat tatttgggaa atttggtatg 1980 aatagtette eetgtgaaca eagateataa aateatatat eaageagaca aataagtagt 2040 agtcacttat atgcttatac ttgtaactta aagtaaaaga attacaaaag catatgacaa 2100 agactaattt taagatatcc taatttaaat tgttttctaa aagtgtgtat accattttac 2160 ctatcatatg aataatttag aaacatgttt ataaaattaa tgtccaaatc cattcaaaag 2220 ttttgtaatg cagatcaccc acaacaacaa agaatcctag cctattaaaa aagcaacacc 2280 acctacatat aatgaaatat tagcagcatc tatgtaacca aagttacaca gtgaatttgg 2340 qccatccaac actitiqagca aagtgttgaa ttcatcaaat gaatgtgtaa tcatttactt 2400 actaatgcca atacacttta aggtaatett aagtagaaga gatagagttt agaatttttt 2460 aaatttatet ettettetaa ageaatagae tteaataaat aaattagaag aateagteat 2520 tcaagccacc agagtatttg atcgagattt cacaaactct aactttctga tacccattct 2580 cccaaaaacg tgtaacctcc tgtcgatagg aacaacccac tgcagggatg tttctcgtgg 2640 aaaaaggaaa tttettttgc attggtttea gaeetaaetg gttacaagaa aaaccaaagg 2700 ccattgcaca atgctgaagt actttttca aatttaaaat ttgaaagttg ttcttaaaat 2760 ctatcattta ttttaaaata cggatgaatg agaaagcata gatttgataa agtgaattct 2820 tttetgeaat etacagacae ttecaaaaat caetacagae actacagaca etacagaaaa 2880 tcataaataa acaagtgcta gtatcaatat ttttaccaaa aaatggcatt cttagaattt 2940 tttatagget agaaggtttg tacaaactaa tetgecaegg attttaaaat atgagtgaat 3000 aaattatatt gcaaaaaaaa tcaggttaca gagaactggc aaggaagact cttatgtaaa 3060 acacagaaaa catacaaaac gtatttttaa gacaaataaa aacagaactt gtacctcaga 3120 tgatactgga gattgtgttg acatattagc attatcactg tcttgctaaa acataaaaat 3180 aaaaagatgg aagatgaaat tacaatacaa atgatgattt aaacatataa aaggaaaata 3240 aaaattgttc tgaccaacta ctaaaggaag acctactaaa gatatgccat ccagcacatt 3300 gecaetetae atgtggtetg taaaceagea geatagggat eetetageta gagt 3354

# **SEL PCT 012.ST25**

<211> 677

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(677)

<223> MAR of chromosome 1 genomic contig; 12803267..12803943

<400> 28

ttatatagta tatataatag tatatattat atagtataca taatagtata tattatatag 60 tatacataat agtatatatt ataatataca taattgtata tatcatatag tatacattat 120 agtatatatc atatagtata cattatagta tatatcatat agtatacatt atatagtata 180 tatcatatag tatacattat agtatatatc atatagtata cattatagta tatatcatat 240 agtatacgta atagtatata tcatatagta tacgtaatag tatatatcat atagtatacg 300 taatagtata tatcatatag tatacgtaat agtatatatc atatagtata cgtaatagta 360 tatatcatat agtatacgta atagtatata tcatatagta tacgtaatag tatatatcat 420 atagtatacg taatagtata tatcatatag tatacgtaat agtatatatc atatagtata 480 tattatatag tatatatcat atagtatata ttatatagta tatatcatat agtatatatt 540 atatagtata tatcatatag tatatattat atagtatata tcatatagta tatataatag 600 tatatatcat atagtatata taatagtata tatcatatag tatatatact atactatatt 660 atatatagta tacataa 677

<210> 29

<211> 332

<212> DNA

# **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(332)

<223> MAR of chromosome 1 genomic contig; 13079684..13080015

<400> 29

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taatatat taatatatta tataattata tataattata tattaattat 180

atatatata ttaatatata attaaaacta tttaattata tgtatattat atataatatg 300

tattatttaa ataataaata tattatttat at

<210> 30

<211> 479

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(479)

<223> MAr of chromosome 1 genomic contig; 15682296..15682774

<400> 30

332

# **SEL PCT 012.ST25**

acaagtacat atatatatag tatatatata caagtacata tatatagtat atatatatat 60 acaagtacat atatatagta tatatatata tacaagtaca tatatatagt atatatatat 120 acaagtacat atatatagta tatatatata caagtacata tatatatagt atatatatat 180 acaagtacat atatatagta tatatatata caagtacata tatatatagt atatatatat 240 acaagtacat atatatagta tatatatata caagtacata tatatatagt atatatatat 300 acaagtacat atatatatag tatatatata tacaagtaca tatatatata gtatatatat 360 atacaagtac atatatatag tatatacaa tatatacaag tacatatata tagtgtatat 420 atatatatac aagtacatat atatacttgt attagtatat atatatat atacaagta 479

<210> 31

<211> 531

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(531)

<223> MAr of chromosome 1 genomic contig; 15694611..15695141

<400> 31

# **SEL PCT 012.ST25**

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<210> 32

<211> 378

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(378)

<223> MAR of chromosome 1 genomic contig; 886276..886653

<400> 32

<210> 33

<211> 595

<212> DNA

<213> Homo sapiens

Seite 37

# **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(595)

<223> MAR of chromosome 1 genomic contig; 3326732..3327326

<400> 33

aaaatatata aatatata aaaatatata aaaatatata aatatata aaaatatata 60 aatatatata aatatatata aaaatatata aatatata aatatata aaatatataa 120 atatatataa aatatatata aatatatata aaaatataaa tatatataaa 180 aatataaata tatataaata tataaaaaa tataaatata tataaatata tataaatata 240 taaatatata taaatatata taaatatata aatatata aatatata aatatatata 300 aatatataaa tatataaaa tatataaaa tatataaata tatataaata tataaatata 360 taaaaatata tataaatata taaatatata taaatatata taaaatata 420 tataaatata tatatata aatatata aatatata taaatatata taaatatata 480 tatatata taaatatata taaatatata tataaatata tataaatata 540 tataaatata tatataaata tatataaata tatataaa tatataaa tatat 595

<210> 34

<211> 738

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(738)

# **SEL PCT 012.ST25**

<223> MAR of chromosome 1 genomic contig; 4485716..4486453

<400> 34 ataatagata atatatatta tatgatagat atataatata ttatataata tataatata 60 tatatatcta tcatataata tatataatat ataatatat atatatctat catataatat 120 aatatatata atatataata tatatcatat tatattgtat ataatatata tcatattata 180 240 aatatatatc atattatatt gtatataata tatatcatat tatattgtat ataatatata 300 360 tattgtatat aatatatat atattatatt gtatataata tatatcatat tatattgtat 420 480 tatcatatta tattgtatat aatatatatc atatattatc tattatattg tatataatat 540 atattatata ttatctatta tattgtatat aatatatat atatattatc tattatattg 600 tatataatat atattatata ttatctatta tattgtatat aatatataat aaatatagta 660 tatataatag ataatatata gtatatatga tatattatat atactatata ttatatatca 720 tatatactat atactata 738

<210> 35

<211> 386

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(386)

<223> MAR of chromosome 1 genomic contig; 5423067..5423452 Seite 39

# **SEL PCT 012.ST25**

<210> 36

<211> 584

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(584)

<223> MAR of chromosome 1 genomic contig; 5805559..5806142

<400> 36

# **SEL PCT 012.ST25**

<210> 37

<211> 345

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(345)

<223> MAR of chromosome 1 genomic contig; 10802644..10802988

<400> 37

<210> 38

<211> 474

<212> DNA

# **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(474)

<223> MAR of chromosome 1 genomic contig; 13496468..13496941

<400> 38

<210> 39

<211> 483

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(483)

<223> MAR of chromosome 1 genomic contig; 2509163..2509645 Seite 42 WO 2005/040377 PCT/EP2004/011974 .

# **SEL PCT 012.ST25**

<400> 39 caaaatacat aatatataat agtattatat aatagtatgt atagttataa tatatagtat	60
aattacaata tatgatatgg tttatatatt atatatagta taatataata taacataata 13	20
ctattataat atataaacta tataatatat actattataa tatatgaact attataatat 18	0
ataaactata tataatatat aatatgtact attataatat ataaactatt ataatataat	40
atataaacta ttataataca taaactatta taatatatat	00
tacattatgt acatactaca ttatgtatta tgtatgtata tatacacaaa atacataata 3	60
tataatagta ttatataata gtatatatag ttataatata tagtataatt acaatatata 42	<u>2</u> 0
atatggttta tatattatat atagtataat acaatataac ataatactat tatatataaa 48	30
cta 483	
.040	
<210> 40	
<211> 641	
<212> DNA	
<213> Homo sapiens	
<220>	
<221> misc_binding	
<222> (1)(641)	
<223> MAR of chromosome 1 genomic contig; 27763492776989	
<400> 40	
tgttatatat atataacata gatattatat atacatgtta tatatataac atagatatta 60	!
tatatacatg ttatatatat aacatagata ttatatatat aacatagata ttatatatac 12	0

atgttatata taacatagat attatatata catgttatat ataacagata ttatatatac 180

### **SEL PCT 012.ST25**

atgttatata taacatagat attatatatg tatgttatat ataacataga tattatatat 240 gtttatataa tatataacat atgtttaaca tatataatat ataacatgtt tatataatat 300 ataacataat tatatgttat atatgatata aaacatatat attatatacg ttatatgtaa 360 tatataacat atattgtata cgttatatgt aatatataac atatattgta tacgttatat 420 gtaatatata acatatattg tatacgttat atgtaatata taacatatat tgcatacgtt 480 atatgtaata tataacatat attgtatacg ttatatgtaa tatgtaacat atattgtata 540 cgttatatgt aatatgtaat atataataca tataacatgt atatataaca tatatgtata 600 taacatatat ataacatata taacatatat gttatattat a 641

<210> 41

<211> 745

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(745)

<223> MAR of chromosome 1 genomic contig; 2858703..2859447

<400> 41

#### **SEL PCT 012.ST25**

<210> 42

<211> 307

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(307)

<223> MAR of chromosome 1 genomic contig; 945522..945828

<400> 42

<210> 43

## **SEL PCT 012.ST25**

<211> 357

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(357)

<223> MAR of chromosome 1 genomic contig; 3402743..3403099

<400> 43

<210> 44

<211> 323

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(323)

<223> MAR of chromosome 1 genomic contig; 3485830..3486152 Seite 46

#### **SEL PCT 012.ST25**

<400> 44
atatttatag actatatatt tatatattta gtgtatttgt atactatata tttatatagt 60
tagtatattt gtatactata tatttatata tttagtatat ttgtatacta tatatttata 120
tatttagaat atttgtatac tatatattta tatatttagt atatttgtat actatatatt 180
tagtatattt gtatactata tatttatata tttagtatat ttgtatacta tatatttata 240
tatttagtat atttatatac tatatactta tatatttagt atatttatat actatatact 300
tatatattta gtatatttat ata

<210> 45

<211> 498

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(498)

<223> MAR of chromosome 1 genomic contig; 3548336..3548833

<400> 45

# **SEL PCT 012.ST25**

aatattaata taatataata taatataat agtatataat attaatatat taatataata 420 gtatataata ttaatgtaat ataatattaa cataatgtat ataataatat aatagtatat 480 aatactaata taatataa 498

<210> 46

<211> 400

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(400)

<223> MAr of chromosome 1 genomic contig; 4595109..4595508

<400> 46

<210> 47

<211> 403

<212> DNA

<213> Homo sapiens

#### **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(403)

<223> MAr of chromosome 1 genomic contig; 7205509..7205911

<400> 47

<210> 48

<211> 309

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(309)

<223> MAR of chromosome 1 genomic contig; 7507280..7507588

<400> 48

#### **SEL PCT 012.ST25**

<210> 49

<211> 516

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(516)

<223> MAR of chromosome 1 genomic contig; 3581085..3581600

<400> 49

atatatatat atatatata atttatatat atatatatta atatatatta tatataaaaa 60 tatataaaat ttatatatat aatttatata tataaaaata tataaaattt atatatataa 120 tttatatata taaaaatata taaaatttat atatataatt tatatatata aaaatatata 180 aaatttatat atataattta tatataaaa aatatataaa atttatatat ataatttata 240 tatataaaaa tatataaaat ttatatatat aatttatata tataaaaata tataaaattt 300 360 aaaattatat atataattat atatataata taaaattata tatataatta tatatataat 420 ataaaattat atatatatg tatatata aaatatacaa aatttatata tataaaatat 480

#### **SEL PCT 012.ST25**

aaaatataca taaaaataaa tatatataat ttatat 516

<210> 50

<211> 534

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(534)

<223> MAR of chromosome 1 genomic contig; 3084851..3085384

<400> 50

atataatata tatgactata tattttatat tatattctat ttcaataaaa tatttatatt 60 120 ttatattata ttttatattt attttatat attttatat attatata atatataatt atatatgcaa taatatatta tatattataa tatataatta tatatgcaat 240 aatatattat atattataat atataattat atatgcaata atatattata gattataata 300 tataattata tatgcaataa tatattatat attatatat agataatata ttaatatata 360 ttataacata taatataa catataatat ataatatat atctaatata taatataaca 420 tataatatat aatatattat ataatatat attacatata taatatatg taatatataa 480 tattacatat atcttcaaaa agagttatgt gtatataata catatatata ccat 534

<210> 51

<211> 583

<212> DNA

<213> Homo sapiens

#### **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(583)

<223> MAR of chromosome 1 genomic contig; 160087..160669

<400> 51

60 atattataca atatattat atattatata taatatattt tatata atat acataatata 120 ttttatatat tatatataat atattttata tataatgtac aatatatttt atatattata 180 240 ttttcatgta acatatatat tttatatata atatatatac catatataat atattttata 300 tataatatat ataccatata taatatatti tatatataat atgtatatca tatatagtat 360 attttatata taataggtat accatatata atatattta tatataatag gtataacata 420 tataatatat titatatata atatgtatac catatataat atatttata tattatagat 480 accatatgta atatacttta tatataatat agataccata tgtaatatac tttatatata atatagatac catatgtaat atactttata tataatatag ata 583

<210> 52

<211> 314

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(314)

# **SEL PCT 012.ST25**

<223> MAR of chromosome 1 genomic contig; 4350424..4350737

<210> 53

<211> 828

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(828)

<223> MAR of chromosome 1 genomic contig; 8443267..8444094

<400> 53

#### **SEL PCT 012.ST25**

ttatatatta tatactatag tatatattat tatatataat agatataata tatataatta 360 420 480 540 600 660 tatatatat atataattat atattatata taatatagta tatataatat gtaattatat 720 atcatataat atataacatt gtatataata tataattaca tattatataa tgtatataat 780 atataattat atacattata taatatagta tataattata tattatgt 828

<210> 54

<211> 573

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(573)

<223> MAR of chromosome 1 genomic contig; 8703190..8703762

<400> 54

# **SEL PCT 012.ST25**

<210> 55

<211> 597

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(597)

<223> MAR of chromosome 1 genomic contig; 8819076..8819672

<400> 55

60 tatatgaaat atacacatat ttttatatat ataatatata tattatatat aatatatgca 120 180 240 300 aatatatata atatatata aatatatata ttatatataa aatatatatt atatgtaaaa 360 tatataatat atataatata tatattatat gtaaaatata tattatatat aaaatatata 420 480 540

# **SEL PCT 012.ST25**

<210> 56

<211> 646

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(646)

<223> MAr of chromosome 1 genomic contig; 759619..760264

<400> 56

60 120 180 240 300 360 420 tataattata tatataatac tatatattat ataattatat ataatactat atattatata 480 acatatatat tatatattat ataataacat atatattata tattataa tacatatata 600 ttatatatta tataatacat tattatataa tatataatat atatta 646

<210> 57

<211> 752

#### **SEL PCT 012.ST25**

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(752)

<223> MAR of chromosome 1 genomic contig; 1226710..1227461

<400> 57

taaacatata tataaatata tataaatata tatataaata tatataaata tataaatata 60 120 aatatatata aatatata taaatatata taaatatata taaatatata taaatatata 180 240 tatataaata tataaatata tataaatata tataaatata tatagaaata tatatagaaa 300 360 420 atatatata atatataaat atatatataa atatatata aaatatatat aaatatatat 480 540 600 660 ataaatatat atataaatac atataaatat atatataaat atatataaat atatatataa 720 atatatata atatatatat aaatatatat aa 752

<210> 58

<211> 300

<212> DNA

# **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(300)

<223> MAR of chromosome 1 genomic contig; 1119049..1119348

<400> 58

<210> 59

<211> 617

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(617)

<223> MAR of chromosome 1 genomic contig; 3603613..3604229

<400> 59

60

#### **SEL PCT 012.ST25**

ataatatata taataaaata tacataatat ataatgtata ataaaatata cataatatat 120 180 240 300 360 420 taaaatatat aatataat atatataata aaatatatat gatatataat atatataata 480 540 ataataaaat atatata 617

<210> 60

<211> 674

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(674)

<223> MAR of chromosome 1 genomic contig; 2592460..2593133

<400> 60

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#### **SEL PCT 012.ST25**

<210> 61

<211> 1694

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1694)

<223> MAR of chromosome 1 genomic contig; 2891680..2893373

<400> 61

#### **SEL PCT 012.ST25**

420 480 aatacatatt aataatatat tattaataag ataatatata totatctata atatatacat 540 atatgtatat gtatgtatat attatagata tacatgttta tacatgtata tattatagat 600 atatacatgt atatacatgt atatattata gatatataca tgtatatacg tatatattat agatatacat gtatatatgt atatatatta tagatataat atatacaaga atataagaat atatataata taatatata tacacataat acgtatatat tatatataca tgtatattat atatglacat atatacatgt atattatata tacatglata ttatatatac atgcatatta tatatatttt tatatataat atccatgtat attatgtata tttgtgtata ttatatatac 900 cacatatatt atatatacat atatattata tatacacata tattatatat acatgtatat 1080 tatatataca cgtatattat atatacacac gtatattata tatacacgta tattatatat 1140 acacacgtat attatatata cacgtatatt atatatacac acgtatatta tatatacacg 1200 tatattatat atacacacgt atattatata tacacgtata ttatatatac acacgtatat 1260 tatatataca cgtatattat atatacacac gtatattata tatacacgta tattatatat 1320 acacacgtat attatatata cacgtatatt atatatacac acgtatatta tatatacatg 1380 tatattatat atacatgtat attatatata cacatgtata ttatatatac atgtatatta 1440 tatatacaca tgtatattat atatgcatgt atattatata tacacatgta tattatatat 1500 acacatgtat attatatata catatatatt atatatacat gtatattatg tatacatata 1560 tattatatat acatgtatat tatagataca tatatattaa atatacatgt atattatgta 1620 tacatgtata cata 1694

<210> 62

<211> 587

#### **SEL PCT 012.ST25**

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(587)

<223> MAR of chromosome 1 genomic contig; 3432560..3433146

<400> 62

gaattatata tatatagctg aattatatac atatataata tatacaatat atattatata 60 120 tttatatatg atatatacaa tatatattac atattatata tacaatatat aatatataat 180 taatattata tattatatat tgtatataat atatattata taacattata taatatatac 240 300 360 atatattatt atatattata tattatata taatatatat tatatatat atatttata 420 480 tatataatat attaatatat ataatatata caatatataa tatataatat ataatatata 540 atataaatta ttatatataa tatatattat atatagctga attatat 587

<210> 63

<211> 313

<212> DNA

<213> Homo sapiens

<220>

# **SEL PCT 012.ST25**

<221> misc\_binding

<222> (1)..(313)

<223> MAR of chromosome 1 genomic contig; 3805392..3805704

<400> 63

<210> 64

<211> 349

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(349)

<223> MAR of chromosome 1 genomic contig; 4521378..4521726

<400> 64

ttatatacac tatataatat gtatttatat atacttatat acactatata tgtatttata 60 tataattata tacactatat aatatgtatt tatatataat tatatacact atataatatg 120 tatttatata taattatata cactatataa tatgtattta tatataattg tatacactat 180

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#### **SEL PCT 012.ST25**

ataatgtata tttatatata attgtataca ctatataatg tatatttatg tataattgta 240 tacactatat aatgtatatt tatgtataat tgtatacact atataatgta tatttatgta 300 taattgtata taccatataa tgtatattta tgtataattg tatatacca 349

<210> 65

<211> 500

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(500)

<223> MAR of chromosome 1 genomic contig; 3240166..3240665

<400> 65

ttaatatata atatatata tatattata tattaatata taatatata tatatataa 60 tatatattat atatttatat tacatatatt tatatgttaa tatatattt atatatttat 180 240 tatatttata ttatatattt atatattgta tttatatatt atatatttat atactatata 300 360 420 atatttatat atattatata tttatatata atatatatta tatattttat ctatatattt 480 atatattaat atatattata 500

<210> 66

<211> 866

#### **SEL PCT 012.ST25**

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(866)

<223> MAR of chromosome 1 genomic contig; 409429..410294

<400> 66

60 aatatataat acatatatta tatatatat atattatata taatatata tacatatatt 120 180 240 300 360 420 480 tatgatatat gatatatatg atatatatga tatatgatat atatgatata tatgatatat 540 600 aatatatgat atatatgata tatgatatgt aatatatg atatattata tataatatat 660 atatgatata tgatatatga tatatatat ataatatata taatatata tatatataat atatataata tataatat ataata 866

# **SEL PCT 012.ST25**

<211> 335

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(335)

<223> MAR of chromosome 1 genomic contig; 614754..615088

<400> 67

<210> 68

<211> 455

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(455)

<223> MAR of chromosome 1 genomic contig; 1299520..1299974
Seite 66

# **SEL PCT 012.ST25**

<400> 68 ggatatatat attattagtt gttatattat tatatattat atatattatt atatataata					
tattatatca tatatattat tatatataat atattatatc atatatat					
tattatatca tatatattat tatatataat atatattata tatattat					
atattatata tattattatg tataatatat atattatata ttatttat					
tatataataa tatataatta attatacata tatacatata taagtataca tataatatat 300					
ttatatagta tatataaata tatatacaat atatttatat attatatat atatataaat 360					
atatacaata tatttatatc atatattta tatatgatac atataatata					
gatatataat atatatcata tatgatatat aacat 455					
<210> 69					
<211> 404					
<212> DNA					
<213> Homo sapiens					
<220>					
<221> misc_binding					
<222> (1)(404)					
<223> MAR of chromosome 1 genomic contig; 19707781971181					
<400> 69					
atatataata tgtataatat ataatatata tcatatattg ttctatgtat attacatata 60					
atatgcatta tatattatat attgcatata atatgcatta tatattatat					
atatgcatta tatattatat attgcatata atatgcatta tatattatat					

#### **SEL PCT 012.ST25**

atatgcatta tatattatat aatatataca catataatat atataattta tatatattta 300 tatatattta catttattat atattatat tatataaata tattttata tatatatat atatatata tatatatata tatatatata tatatatata tata

<210> 70

<211> 605

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(605)

<223> MAR of chromosome 1 genomic contig; 3562918..3563522

<400> 70

60 120 acatataata tatatgatat ataatacata tataatatat atgatatata atacatatat 180 aatatatatt atatataata catatataat atatattata tataatacat atataatata 240 300 ataatacata tataatata attatataat acatgtatat aatatatat atataata 360 catatatatt atataataca tgtatataat atatattata tataatacat atatattata 420 aatattatat ataatacata tattatatat aatataaata tatataatac atatataata 540 cacatattat atataataca tatattatat ataatatata tattatatat aatatatat 600 taata 605

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# **SEL PCT 012.ST25**

<210> 71

<211> 317

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(317)

<223> MAR of chromosome 1 genomic contig; 189743..190059

<400> 71

<210> 72

<211> 522

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(522)

## **SEL PCT 012.ST25**

<223> MAR of chromosome 1 genomic contig; 229111..229632

<400> 72 gatatatata tttatatata taaaagatat atattattta tatataaaga tatatattta 60 tatatataaa agatatatat tattatata tataaaaagat atatatttat atatatgata 120 180 240 300 tttatatata aaagatatat attatttata tatataaaag atatacatat aaaagatata 360 tattatata taaaagatat atatattat atataaaaga tacatatatt tatatatata 420 480 tatatatat ttttatatat aaaagatata tataaatata ta 522

<210> 73

<211> 1110

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1110)

<223> MAR of chromosome 1 genomic contig; 1138030..1139139

<400> 73

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## **SEL PCT 012.ST25**

180 attatatota tattatotat acataatata ttatatatta tatgtatatt atgtatacat 240 aatatattat atattatatg tatattatgt atacataata tattatatat tatatgtata 300 360 attatatgta tattatgtat acataatata ttatatatta tatgtatatt atgtatacat 420 aatatattat atattatatg tatattatgt atacataata tattatatat tatatgtata 480 540 attatatota tattatotat acataatatt tatatattat atgtatatta tgtatacata atatattata tattatatgt atattatgta tacataatat gtacacataa tatttatata 600 ttatatgtat attatgtata cataatattt atatattata tgtatattat gtatacataa 660 720 tatttatata ttatatgtat attatgtata cataatattt atatattata tgtatattat 780 gtatacataa tatttatata ttatatgtat attatgtata cataatatat tatatattat 840 atotatatta totatacata atatattata tattatatgt atattatgta tacataatat 900 attatatatt atatgtatat tatgtataca taatatttat atattatatg tatattatgt 960 atacataata tattatatat tatatgtata ttatgtatac ataatatatt atatattata tgtatattat gtatacataa tatattatat attatatatg tatattatgt atacataata 1020 tattatatat tatatatgta tattatgtat tatattatat attatgtata ttatagatta 1110 tgtatgcata cataatatgt attgtatatt

<210> 74

<211> 521

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(521)

#### **SEL PCT 012.ST25**

<223> MAR of chromosome 1 genomic contig; 2863407..2863927

<400> 74 aatatatata aatatataaa tatatataaa tatatataca tataaatata taaatatata 60 120 taaatatata taaatatatg taaatatata taaatatacg taaatatata aatatatat 180 actatatata aatatata aatataaata tataaatata tataaatata tataaatata 240 taaataaata catataaata tataaataaa tacatataaa tatataaaa tatataaaaa 300 tatatataaa tatatatata aatatataaa catatataaa tatataaata tatataaata 360 tataaataca taaaatatat aaatatata aaatatataa atatataa atatagataa 420 atatagataa atatataaat atataaaat atataaatat agataaatat ataaatatat 480 aaatataaat atataaaaat atataaaaat a 521

<210> 75

<211> 560

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(560)

<223> MAR of chromosome 1 genomic contig; 5712303..5712869

<400> 75

**SEL PCT 012.ST25** 

<210> 76

<211> 479

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(479)

<223> MAR of chromosome 1 genomic contig; 8578812..8579290

<400> 76

#### **SEL PCT 012.ST25**

atatacacac tatatataat atatattata tatagttaaa tataggtat atgcaattag 420 atataggta tatgtaatta tatataggt atataggta tatgtaatta 479

<210> 77

<211> 477

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(477)

<223> MAR of chromosome 1 genomic contig; 8579294..8579770

<400> 77

<210> 78

<211> 331

<212> DNA

<213> Homo sapiens

## **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(331)

<223> MAR of chromosome 1 genomic contig; 8580024..8580354

<400> 78

actatatgtt atatacataa gatatagtat ataccatata ttatatacat tatatatagt 60

gtatactata tataatgtat ataatatata gtatatatac actatatata ctatgtatat 120

atacactata tatactatgt atatatacac tatatatact atgtatatat acactatata 180

tactatgtat atatacacta tatatactat gtatatata actatatata ctatgtatat 240

atacactata tatactatgt atatatacac tatatatact atgtatatat agtgtatata 300

tactgtatat gttatagtgt atatatagta t 331

<210> 79

<211> 410

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(410)

<223> MAR of chromosome 1 genomic contig; 8580705..8581114

<400> 79

tatagtctat attatataca gtctatataa tatatagtat atactatata tacttttcct 60

#### **SEL PCT 012.ST25**

<210> 80

<211> 433

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(433)

<223> MAR of chromosome 1 genomic contig; 12979167..12979599

<400> 80

# **SEL PCT 012.ST25**

<210> 81

<211> 385

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(385)

<223> MAR of chromosome 1 genomic contig; 16336644..16337028

<400> 81

<210> 82

<211> 363

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

## **SEL PCT 012.ST25**

<222>	(1)	)(	(36)	3

<223> MAR of chromosome 1 genomic contig; 20624448..20624810

<400> 82

tatatatata gitatatata tatitatata tatagitata tatatatiti tatatagita 60
tatatatata gitatatata gitatatata tatagitata tatatagita tatatatagi 120
tatatatata tagitatata tatagitata tatatagita tatatatagi tatatatata 180
tagitatata tatagitata tatatatagi tatatatata gitatatata tatagitata 240
tatatagita tatatatagi tatatatata gitatatata tatagita 300
tatatatata gitatatata tatagitata tatagitata tatatagita 360
tagi

<210> 83

<211> 310

<212> DNA

<213> Homo sapiens

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<221> misc\_binding

<222> (1)..(310)

<223> MAR of chromosome 1 genomic contig; 566025..566334

<400> 83

#### **SEL PCT 012.ST25**

<210> 84

<211> 1236

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(1236)

<223> MAR of chromosome 1 genomic contig; 1171429..1172664

<400> 84

aaagtattat atgtattata tgtatatgta ttatatatta catatgtatt atatataata 60 attatatagt atatagta tatataatgt attatatatt atatagtata tatagtatat 180 ataatgtatt atatatagta tatataatgt attatatagt atatatacta tataatgtat 240 tacatattat gtatagtata tgtaatgtat tatatattat atagtatatg taatgtatta 300 360 tgtattatat aacatatata atatatatga tgtattatat agcatgtata gtatatatga 420 tgtattatat agcatgtata gtatatatga tgtattatat atagcatgta tagtatatat 480 gatgtattat atatagcatg tatagtatat atgatgtatt atatatagca tgtatagtat 540 atatgatgta ttatatatag catgtatagt atatatgatg tattatatat agcatgtata 600 gtatatatga tgtattatat atagcatgta tagtatatat gatgtattat atatagcatg 660

## **SEL PCT 012.ST25**

tatagtatat atgatgtatt atatatagca tgtatagtat atatgatgta ttatatatag 720 catgtatagt atatatgatg tattatatat agcatgtata gtatatatga tgtattatat 780 attatatatg gtatatatga tgtattatat attatatatg gtatatatga tgtattatat 840 900 attatata atatataga tgtattatat atgatgtatt atatataata tatatgatgt 960 attatatata ttattatcta ttatatacga tgtattatat gcaagttatt atgtataata tataatgtat tatatattat ataatgtata atatataaat ataaatat ataattatgt 1080 ataaatatag aaatatatac attatacatt atatacatta taatgtataa tatataaata 1140 tattatata aaatgtatac attatatata aatatattat atacattata tataaaatat 1200 gtatatagtt attatacctt atatatacta aacagt 1236

<210> 85

<211> 309

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(309)

<223> MAR of chromosome 1 genomic contig; 1925173..1925481

<400> 85

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**SEL PCT 012.ST25** 

aatgtatat

309

<210> 86

<211> 312

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(312)

<223> MAR of chromosome 1 genomic contig; 4396756..4397067

<400> 86

cacagtgtat atatagtata tatactgtat atatactgtg tatatacact gtatatacac 60

agtgtatata cagtatatat actatatata cactgtgtat atatagtata tataaattct 120

aggaatatat atactatat atataaattc taggaatata tacacactat 180

acactatata tacacgagat atataacata tacactatat actatacata acatatatac 300

tatatatact at

312

<210> 87

<211> 398

<212> DNA

<213> Homo sapiens

<220>

# **SEL PCT 012.ST25**

<221> misc binding

<222> (1)..(398)

<223> MAR of chromosome 1 genomic contig; 56057..56454

<400> 87

<210> 88

<211> 391

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(391)

<223> MAR of chromosome 1 genomic contig; 56984..57374

<400> 88

# **SEL PCT 012.ST25**

<210> 89

<211> 309

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(309)

<223> MAR of chromosome 1 genomic contig; 469547..469855

<400> 89

atatgttata tataatatat atgttatata tacgttatat gttatatat atgttatatat 120

tatatattat atataatata taatatatgt gatatataat ataaaatata tgtgatatat 300

attatatat 309

<210> 90

<211> 441

<212> DNA

# **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(441)

<223> MAR of chromosome 1 genomic contig; 546190..546630

<400> 90

atacacaaca tatgtgtata tatatagtat atatacacaa catatgtgta tatatatagt 60 atatatacac aatatatgtg tatatatat gtatatatac acaatatatg tgtatatata 120 gtataaatat atactatata tagtatatat agtataaata tatactatat atagtatata 180 catagtataa atatatacta tatatagtat atacatagta taaatatata ctatatatag 240 tatatacata gtataaatat atactatata tagtatatac atagtataaa tatatactat 300 atatagtata tacatagtat aaatatatac tatatatagt atatacatag tataaatata 360 tactatatat agtatataca tagtataaat atatactata tatagtatat acatagtata 420 aatatatact atatatagta t 441

<210> 91

<211> 1367

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(1367)

<223> MAR of chromosome 1 genomic contig; 124643..126009 Seite 84

# **SEL PCT 012.ST25**

## **SEL PCT 012.ST25**

<210> 92

<211> 458

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(458)

<223> MAR of chromosome 1 genomic contig; 58908..59365

<400> 92

tatatgatat atatgatata tatgggatat atatgatata tatgatatat atggtatata 60 120 180 240 atatatgata tatatggtat atatggtata tatatgatat atatgatata tatggtatat 300 atatgatata tatgatatat atggtatata tatgatatat atgatatata tggtatatat 360 420 tatatatag atatataga tatatatat atatagg 458

<210> 93

<211> 330

<212> DNA

<213> Homo sapiens

<220>

SEL PCT 012.ST25	
<221> misc_binding	
<222> (1)(330)	
<223> MAR of chromosome 1 genomic contig; 30686730719	6
<400> 93 ataatatata aatatatatg atatatatct atatatatca tatataaata tatatgatat	60
atatctatat atatcatata taaatatata tgatatataa atatatatga tatatatcta	120
tatatatcat atataaatat atatgatata taaatatata tgatatatat	180
catatataaa tatatatgat atatatctat atatcatata taaatatata tgatatatat	240
ctatatatat catatataaa tatatatgat atctatctat atatatcata tataaatata	300
tatgatatct atctatatat atcatatata 330	
<210> 94	
<211> 353	
<212> DNA	
<213> Homo sapiens	
<220>	
<221> misc_binding	
<222> (1)(353)	
<223> MAR of chromosome 1 genomic contig; 636899637251	
<400> 94 tatgtataca tatacacata tacgtatata tatacatata tacacatata cgtatatata	60
tacgtataca tacatatgta tatgtatacg tatacacaca tatgtatatg tatacgtata	120

Seite 87

cacacatata cgtatatatg tatacgtata cacacatata cgtatatgta tacatatata

120

180

# **SEL PCT 012.ST25**

tgtgtacata tacgtatata cgtatatgta tacatatata cgtttatgta tatatacgta 240 tatacgtata tatgtatatg tatacatata tacatatatg tgtatatacg tatatacgta 300 tatgtgtata tatacaatat acatacatgc acatatatgt gtatatgcac ata 353

<210> 95

<211> 345

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(345)

<223> MAR of chromosome 1 genomic contig; 1435510..1435854

<400> 95

<210> 96

<211> 521

<212> DNA

<213> Homo sapiens

#### **SEL PCT 012.ST25**

<220>	•
<221>	misc_binding
<222>	(1)(521)
<223>	MAR of chromosome 1 genomic contig; 3969540215

tatatatata atagatatta tatatctatt atatatata atagatatta 60 tatatctatt atatataa tagatattat atatctatta tatatataat agatattata 120 tatctattat atataatata tatctattat atattatata tctattatat ataatata 180 tctattatat atattatata tctattatat atataataga tattatatat ctattatata 240 300 360 tatattatat atctattata tataatatat atctattata tatattatat atctattata 420 tatattatat atctattata tataatatat atctattata tatattatat atctattata 480 tataatatat attatatat tattatatat tgtatatcta t 521

<210> 97

<400> 96

<211> 484

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(484)

<223> MAR of chromosome 1 genomic contig; 1286007..1286490

# **SEL PCT 012.ST25**

<400> 97 atatcatata tattatatat catatatatg atatataaaa attatatatc atatatatga 60 tatatataa tatatatat catatataat atatataata tattatatat ataaattata 120 tataatatta tataaaatt atatatcaca tatatgacat ataaattata tatcacatat 180 atgatatata atttatatat cacatatatg atatataatt tatatatcat atatatgata 240 tataatttat atatcatata tatgatatat aatttatata tcatatata gatatatata 300 360 aatatatata atattatata atatagaata ttatatatta tatattacat attatataat atat 484

<210> 98

<211> 244

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(244)

<223> MAR of chromosome 1 genomic contig; 73556..73879

<400> 98

# SEL PCT 012.ST25 244

aata

<210> 99

<211> 463

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(463)

<223> MAR of chromosome 1 genomic contig; 179038..179500

<400> 99

<210> 100

<211> 390

<212> DNA

<213> Homo sapiens

#### **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(390)

<223> MAR of chromosome 1 genomic contig; 55617..56006

<400> 100

<210> 101

<211> 582

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(582)

<223> MAR of chromosome 2 genomic contig; 1157405..1157986

<400> 101

tgtatatgta tatatacaca tacgcacata tatgtatatg tatatataca catacgcaca

60

#### **SEL PCT 012.ST25**

tatatgtata tgtatatata cacatacgca catatatgta tatgtatatg tatatgtata 120 tatacacata tacacatata tgtatatgta tatatacaca tatacacata tatgtatatg 180 tatatataca catatacaca tatatgtata tgtatatata cacatacaca tatatgtata 240 tgtatatgta tatatacaca tacacatata tgtatatgta tatgtatata tacacatata 300 cacatatata catatatgta tacatatatg tgtatatata tacacatata tatacatata 360 420 tgtatgtata tatacacata tacatatata tgtatatgtg tatatatatt agacagatat 480 atatgtacat atacatatat atgtatatgt atatgtatat gtatatgtat atgtatatgt atatgcatat ataatataca tatacatata tgtatatgta ta 582

<210> 102

<211> 322

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(322)

<223> MAR of chromosome 2 genomic contig; 1858638..1858959

<400> 102

#### **SEL PCT 012.ST25**

#### ccatatatat acaccatata ta

322

<210> 103

<211> 914

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(914)

<223> MAR of chromosome 2 genomic contig; 5712196..5713109

<400> 103

aaatatatat totatatata gaaaatatat attotatata tatagaatat atatagaata 60 tatattctat atatattcta tatatataga atatatatat aaaacatata ttctatatat 120 aaaatatata ttctatatat ataaaatata tattctatat atatagaatg tatataaaat 180 atatattcta tatataga atgtatataa aatatatatt ctatatatat agaatgtata 240 taaaatatat attotatata tatagaatgi atataaaata tatattotat atatagaa 300 tatatataac atatataga aatatatata aaatatatat aaatacatat ttctatatat 360 420 480 540 600 aaattatata taaatatata ttcatatata taatatata aaatatttat ttcatatata 660 aaatatattt aaatatatat ttotatatag aatatatatt otatatataa aatatatata 720 780

#### **SEL PCT 012.ST25**

tatatatat atatatata atatatat atataaaata tatatacaat atatattata 840 tatatatata tatagaatat atattaacat atatttcaat atattaatat atgaaatata 900 tataaatatt tcat 914

<210> 104

<211> 370

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(370)

<223> MAR of chromosome 2 genomic contig; 5713613..5713982

<400> 104

<210> 105

<211> 442

<212> DNA

<213> Homo sapiens

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# **SEL PCT 012.ST25**

<220> <221> misc\_binding <222> (1)..(442) <223> MAR of chromosome 2 genomic contig; 7481647..7482088 <400> 105 atataaatta tataatatgt tatataatat ataaatatat tatataacat gttatataat 60 120 taacatgtta tataatatat tatgtaatat gttatataat atataatata ttatataaca 180 tgttatataa tatataacat gttatataat atgttatata atatataaat atattatatt 240 atatgttata taatatata atatattata ttatatgtta tataatatat aaatatatta 300 tattatatgt tatataatat ataaatatat tatattgtat gttatataat atataaatat 360 attatattgt atgttatata atatataaat atattatatt gtatgttata taatatataa 420 atatattata ttatatatgt ta 442 <210> 106 <211> 338 <212> DNA <213> Homo sapiens <220> <221> misc\_binding

<222> (1)..(338)

<223> MAR of chromosome 2 genomic contig; 9594557..9594894

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<400> 106

<210> 107

<211> 364

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(364)

<223> MAR of chromosome 2 genomic contig; 10519720..10520083

<400> 107

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# **SEL PCT 012.ST25**

<210> 108

<211> 342

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(342)

<223> MAR of chromosome 2 genomic contig; 11481943..11482284

<400> 108

atatgtaata tatatcatat atatgtaata tatatcatat at 342

<210> 109

<211> 415

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(415)

#### **SEL PCT 012.ST25**

<223> MAR of chromosome 2 genomic contig; 13499598..13500012

<400> 109

<210> 110

<211> 330

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(330)

<223> MAR of chromosome 2 genomic contig; 16370976..16371305

<400> 110

catttacata tgtatgtata agtatgtata ttacatactt atacatacat acttataaat 60
atataagtat aatacataca tacttataaa tatataagta taatacatac atacttatac 120
atatataagt ataatacata catacttata catatataag tataatacat acatacttat 180
acatatataa gtataataca tacatactta tacatataag tataatacat acatacttat 240

#### **SEL PCT 012.ST25**

acatatataa gtataataca tacatactta tacatatata agtataatac atacttatta 300 catatgtata taagtatatt acatacttat 330

<210> 111

<211> 702

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(702)

<223> MAR of chromosome 2 genomic contig; 626641..627342

<400> 111

60 120 180 240 300 360 420 480 540 600 tattatatat atacatatat attatatata catatattat atatacatat atattata ta 660 tacatatata tittatatat atataatata tattitatat at 702

#### **SEL PCT 012.ST25**

<210> 112

<211> 679

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(679)

<223> MAR of chromosome 2 genomic contig; 3196047..3196725

<400> 112

atatattata tattcatata tcataaatat atatattata tattcatata ttatatatct 60 atatattat atattcatat attatatatc tatatatta tatattcata tattatatat 120 ctatttatat attcatatat tatatatcta tatattttat atattcgtat attatatatc 180 tatatattat atattcgtat attatatatc tatatattat gtattcatat atatctatat 240 attatatata ticatatata tiataaatta tattaatata giatatatot attataaatg 300 tatattcata tagtatatat ctatatatta taaatataca tatattatat atttatatat 360 tatatatca tatagatcta tatattatat atattcatat atgaatatat atattatatg 420 tatatatat ataaatatat ttatatagta tagatattat atagtatatg catatttata 480 ttataaataa tttacatagt atatgtatat ttataaatta tatatattta catattacat 540 gtatatttat atattataaa tacatattta catattataa atatattat atattatgaa 600 tataatttat atattattac atatttacat atatgcatag ttatatatta taaatatgca 660 tttatgtaaa tatatattt 679

<210> 113

<211> 728

#### **SEL PCT 012.ST25**

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(728)

<223> MAR of chromosome 2 genomic contig; 3196778..3197505

<400> 113

tacataaata tatatttaca atatgtaaat atctgatatg taaatatgta tttataatat 60 ataaatatac atataatatg taaatatata aatatacata tactatgtaa atatatgtta 120 180 tatatacata tactatataa atatagaata tataaatata catatactat ataaatatgt 240 aatatataaa tatatactat ataaatatac atatactata taaatgtatt tataatatat 300 aaatatacat atactatata aattcatata tgaatatata atatataaat atatataata tatgaatata tactcatata taaatatata tgaatatata tttataatat atagatataa 360 agatatatac catatgaata tatattatac actatatgaa tatatatta taatatataa 480 atagatatat actatatgaa tatataatat atatactcta tgaatatata atatatatac 540 tatatgaata tattatatac tgtatgaata tataatatat agatgtatac tatatgaata 600 tataatatat agatatatat actatatgaa tatatataat atatagatat atactatatg 660 aatatatatg atatatagat atatactata tgaatatata atatatagat atatattat 720 728 gatatatg

<210> 114

<211> 413

<212> DNA

# **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(413)

<223> MAR of chromosome 2 genomic contig; 2560638..2561050

<400> 114

atataaatat atattatat attttatata aatatatata tttatatatt tttatataaa 60

tatatatatt tatataatt tatataaata tatatattta tatatattta tataaatata 120

ataaaatata taaatatctt tatatataaa tatataaaat atataaatat ctttatatat 300

aaatatataa aatatataaa tatatttata tataaatata taaaatatat aaatatattt 360

<210> 115

<211> 361

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(361)

<223> MAR of chromosome 2 genomic contig; 4965309..4965669

#### **SEL PCT 012.ST25**

<400> 115 tatacgtata tatacatata tatacgtata tatatacata tatata	acgta tatatacata	60
tgtatatatg tgtgtacatg tatatatata catatgtaca tatata	tgta cacatatata	120
tatacatata tatgtacaca tatacatata tatgtacaca tatac	catata catatatatg	180
tacacatata tatacatata tatgtacaca catatatata cata	tatatg tacacacata	a 240
tatacgtata tatgtacaca catatatacg tatatatatg tacac	cacata tatacgtata	300
tatatgtaca cacatatata tacgtatata tatgtacaca tatat	atata cgtatatata	360
t 361		

<210> 116

<211> 325

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(325)

<223> MAR of chromosome 2 genomic contig; 5258150..5258474

<400> 116

tacacacaca tatacatata tacatatata cgtgtatacg tatacgtata tacgtatata 60
tacatatatg tatacgtata cgtatatacg tatatataca tatatgtata cgtatacgta 120
tatacgtata tatacatata tgtatacgta tacgtatata cgtatatata catatatgta 180
tacgtatacg tatatacgta tatatacata catatgtata cgtatacgta tatatgtata 240
tatacgtata tgtatacgta tacatatata cgtatatata cgtatatgta tatgtatata 300
cgtatatgta tatatgtaca tatac 325

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. . . . . . .

<210> 117

<211> 1508

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(1508)

<223> MAR of chromosome 2 genomic contig; 6057499..6059006

<400> 117

60 taatatata attaattata taatatata aaattatata atatataaat taattatata 120 180 atacaaatta tatactatat taattatata ttatataatt aattatata tatatataa 240 ttatatatta ttaaattaat tatataatat ataaattata taatatata attaattata 300 360 420 480 tacatcatat atatcacata tagattatat aatagttata tattatataa taaattatat 540 ataatatata ataaacatat ataacatatg ttatatata cataatatag tataatata 600 aacatatgtt atatattaca taatatagta taatatataa catgttatat attacataat 660 atagtataat atataacata tgttatatat tacataatat agtataatat ataacatatg 720 ttatatatta cataatatag tataatatat aacatatgtt atatattaca taatatagta 780 taatatataa catatgttat atattacata atatagtata atatataaca tatgttatat 840

# **SEL PCT 012.ST25**

attacataat atagtataat atataacata tgttatatat tacataatat agtataatat 900	)
ataacatatg ttatatatta cataatatag tataatatat aacatatgtt atatattaca 960	)
taatatagta taatatataa catatgttat atattacata atatagtata atatataaca 102	20
tatgttatat attacataat atagtataat atataacata tgttatatat tacataatat 1080	
agtataatat ataacatatg ttatatatta cataatatag tataatatat aacatatgtt 1140	)
atatattaca taatatagta taatatataa catgttatat attacataat atagtataat 1200	)
atataacata tgctatatat tacataatat agtataatat atatgttata tattacataa 1260	)
tatagtataa tatataacat atgttatata ttacatatta tagtataata tatatgttat 1320	
atattatata atatagtata atatataatg tatgttatat attatataat atagtataat 1380	
atataacatg ttatatatta tataatatag tataatatat atgttatata ttatataata 1440	
tagtataata tataatatat gttatatatt atataatata gtataatata tatgttatat 1500	
attatata 1508	

<210> 118

<211> 415

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(415)

<223> MAR of chromosome 2 genomic contig; 7996866..7997280

<400> 118

caattatata atatacatat tatataattg tataaattat acaatcatat aattatata 60 tatataatat acatataata taattatata taattatata attttataat ataattatat 120

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#### **SEL PCT 012.ST25**

<210> 119

<211> 526

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(526)

<223> MAR of chromosome 2 genomic contig: 8300930..8301455

<400> 119

tatatcatat gatatattat acaatatatc atataatatg atatattata tgatatattg 60 tacaatatat catatgatat atgatatatt atacaatata tcatataagg tatatattat 120 atcatatata atatataata taatatatga tataatatat gatatatgat atataatata 180 tgatatatga tatatgatat ataatatatg atatatgata tatgatatat aatatatgat 240 atatgatata tgatatata tatatgatat atgatatatg atatgatata tgatatatga 300 tataatatat gatataatat atgatatata ttatatgata tataatatat gatataattt 360 atatgatata taatataga tatataatat ataatatag atatgatata tattatatca 420 tatataatat ataatataat atatgatata tattatatat ttttatacat tatatatata 480 aactatataa caatataaca tattatgtgt ataatatata ttacat 526

# **SEL PCT 012.ST25**

<210> 120

<211> 402

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(402)

<223> MAR of chromosome 2 genomic contig; 8576553..8576954

<400> 120

<210> 121

<211> 477

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

# **SEL PCT 012.ST25**

<222> (1)(477)
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<223> MAR of chromosome 2 genomic contig; 8785649..8786125

<400> 121

60 tatttatata tatatttata tatatattta tatatattta tatatatat tatatatata tttatatata tatttatata tttatatata tatatttta tatatttata tatatatta 120 tatatttata tatatttata tttatatata tatttatata tatttatata tatttatata 180 tatatattta tatatattta tatatatata tttatatata tttatatata tttatatata 240 300 tatatatata ttcatatata tttatatata tatttatata tatatttata tatatttata 360 420 tatatttata tatatatta tatatatatt tatatatata tatttatata tatatttata tatatatatt tatatatata tttatatata tatatttata tatatatta tatatat 477

<210> 122

<211> 773

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(773)

<223> MAR of chromosome 2 genomic contig; 10064737..10065509

<400> 122

Seite 109

#### **SEL PCT 012.ST25**

ttgtatataa tatattatat tgtatatatt atattgtata tattatattg tatacaatat 180 240 tattatattg tatattat attgtatata atatattata ttgtatataa tatattatat 300 tgtatatatt atattgtata taatatatta tatgtatata atatagtgta tactatatta 360 tataatatat attataca atatataata tattgtatat catatatgat atattgtata 420 taatatataa tatatgatat attgtatata atatattata tatgatatat tgtatattat 480 atattatata tgatatattg tatattatat attatatatt gtatattgta tattatatat 540 tatatattgt atataatatg ttatatattg tatataatat gttatatatt atatattgta 600 tatatgttat atattatgta ttgtatataa tatgttatat attatatatt gtatataatg 660 tattatatat tatatatat atatattgta tataatgtat tatatattgt atattatata 720 773

<210> 123

<211> 1554

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(1554)

<223> MAR of chromosome 2 genomic contig; 1039775..1041328

<400> 123

ataatatatt aaatgtatat ataatatatt aaatataaat atattataa tatataaata 60 tttatataaa tataaaatat atattaaata taaatatata taaaatatat ataaaatata 120 taaaatataa atatatata aatatatat aaatatata aatataaata tatattaaat 180

# **SEL PCT 012.ST25**

atattttaaa tatataaaat ataaatatat attaaatata ttttaaatat attaaatata 240
aatatatatt aaatatatt taaatatatt aaatataaat acatatatta aatatatat
atatatataa aatatataaa atataaatat atattaaata tatataaaat atatatgtta 360
aatatataaa agatatataa aatataaata tatattaaat atatataaaa tatatatata 420
ttaaatatat atattaaata taaatatata taaaatataa atatatgtat taaatatata 480
tattaaatat aaatatatgt attaaatata tattaaatat gaatatatgt attaaatata 540
tattaaatat aaatatatgt attatatata tagaatataa atatatgtat taaatatagt 600
atattaaata taaatatat taaaatatat attaaatatg aatatatat
attaaaaata tatataatat aaatatata taataaaaat atatataata
taaatatata taaaatatat atattaaaaa tatatataaa atatatatat taaaaatata 780
tataaaatat atatattaaa aatatatata aaatatatat attaaaaata tatattaaat 840
ataaatatat atattaaaaa tatatattaa atataactat atattaaata tatattaaat 900
ataactatat attaaatata tattaaatat aactatatat taaatatat ttaaatataa 960
ctatatatta aatatatt aaatataact atatattaaa tatatattaa atataactat 1020
atattaaata tatattaaat ataactatat attaaatata tattaaatat aactatatat 1080
taaatatata tgaaatataa ctatatatta aatatatatt aaatataact atatgtatta 1140
aatataaata tatgtottaa atatatatta aatataaata tatgtattaa atatatat
aatataaata tgtgtattaa atatatatta aatataaata tgtgtattaa atatatat
aatataaata tgtgtattaa atatatatta aatataaata tgtgtattaa atatctatat 1320
taaatataaa tatatgtatt aaatatatat taaatataaa tatatattaa atatatatat 1380
taaatataaa tatatattaa atataaatat atatattaaa tatatatat aaatataaat 1440
atatataaaa tatatatat aaatataaat ataaatataa aatatatat aaatataaat 1500
acatatatta aatatatgta ttaaatatat atataaaata tatgtattaa atat 1554

<210> 124

<211> 650

#### **SEL PCT 012.ST25**

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(650)

<223> MAR of chromosome 2 genomic contig; 3944813..3945462

<400> 124

catgatatat tatgtataat atatattata gattacatat aaattatata tataatatat 60 aattatataa tatataatat tatataatat attatatata ttatacaatt atataatata tataatatac aattataa tatataatat acaattatat aatatataa acaatataat 180 atatatttaa tatattatat aatacatatt taatatatta tatattatat gttatatact aaatatataa tatgtattta atatatacta ttatatatgt aatatattat ataatttatg 300 taacatatta tatattatat atgcaatata ttacatgtta catatatat acatataata 360 tatgtaatat ataatataca ctatattatt atagtatata atatactata ttatgtaatt 420 atataatata gtatattata cactatatta tattatcata taattatata ttatatacta 480 tattacatat atattatgta atataatatg caatatgtta catatataat atatatgtat 540 tatatagtat atatactata gtatatataa aatatatgct ataatatata ttttatatat 600 tatataatac atataatgta tcatatatta tatataatat attttataat 650

<210> 125

<211> 441

<212> DNA

<213> Homo sapiens

#### **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(441)

<223> MAR of chromosome 2 genomic contig; 5314265..5314705

<400> 125

<210> 126

<211> 1169

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(1169)

<223> MAR of chromosome 2 genomic contig; 5953971..5955139

<400> 126

# **SEL PCT 012.ST25**

atgtattcat attatatatt tatatataaa taatatacat tcatattata tatttatata 60 taaataatat atattcatat tatatattta tatataaata tataatatat ttatgtataa 120 180 240 300 360 420 cttatatata aataatatat attcatatta tatatttata taaaaataat atatattcat 480 atattatata tttatatata aataatgtat attcatatta tatattata tataaataat 600 660 atatatattc atattatata titatatata aatatatatt catattatat atttatataa 720 780 ataatata tattcatatt atatatttat atataatata tatattcata ttatatattt 840 900 ttatatattt atataaaat aatgtatatt catattatat atttatatat aaatatatat attcatatta tatatttgta tataaatata tattcatatt atatatttgt atatatattc 1020 atatatattt atatataaat atataatatt catattatat ataaatatat atattcatat 1080 attcatatta tttatatata taaataata 1169

<210> 127

<211> 653

<212> DNA

<213> Homo sapiens

# **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(653)

<223> MAR of chromosome 2 genomic contig; 6427669..6428321

<400> 127

tatatatgta tacatatatg tatatatgtg tatatatgta tacatatatg tatatatgtg 60 tatatatgta tacatatatg tatatatgtg tatatatgta tacatatatg tatatatgtg 120 tatatatgta tacatatatg tatatatgtg tatatatgta tacatatatg tatatatgtg 180 240 tatatatgta tacatatatg tatatatgtg tatatatgta tacatatatg tatacatgtg 300 tacatgtgta tacatatatg tatacatgtg tacatgtgta tacatatatg tatacatgtg 360 tacatgtgta tacatatatg tatatatgtg tatacatata tgtatatatg tgtatatatg tatacatata totatataag totatatato totatatota tataagtota tatatotota 420 tatgtatata agtgtatata tgtgtatatg tatataagtg tatatatgtg tatatatgta 480 tacatatatg tatatatgtg tatatatgtg tatatgtata taagtgtata tatgtgtata 540 600 tatgtataca tatatatgtg tatatatgta tacatatatg tatatatgtg tatatatgta tacatatatg taaatatgtg tatatatgtg tatatgtata taagtgtata tat 653

<210> 128

<211> 414

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(414)

# **SEL PCT 012.ST25**

<223> MAR of chromosome 2 genomic contig; 10890453..10890866

<210> 129

<211> 496

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(496)

<223> MAR of chromosome 2 genomic contig; 13952568..13953063

<400> 129

#### **SEL PCT 012.ST25**

atatacatat tatatattat atattgtata tataatatac atattatata ttatatattg 300 tatatataat atacatatta tatattatat attgtatata taatatacat attatatatt 360 atatattgta tatataatat acatattata tattatatat tgtatatata atatacatat 420 tatatattat atattgtata tataatatac atattatata ttatatattg tatatataat 480 atacatatta tatatt

<210> 130

<211> 317

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(317)

<223> MAR of chromosome 2 genomic contig; 16942865..16943181

<400> 130

tctcctagta gttatatata tatatatgtg tatatatata tatcctagta gatatatata 60

tatatatatc ctagtagata tatatatat tatatcctag tagatatata tatatatata 120

tcctagtagt tatatatata tatatatcct aacagttata tatatatata tcctagtagt 180

tatatatata tatatcctag tagttatata tatatatat tcctagtagt tatatatata 240

tatatcctag tagttatata tatatatatc ctagtagtta tatatata ttatatatta 300

tataatatat atataat 317

<210> 131

<211> 464

<212> DNA

Seite 117

# **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(464)

<223> MAR of chromosome 2 genomic contig; 17217049..17217512

<400> 131

acatactata tatatacaca tactatatat actatataca gtatatagta tacatatact 60 atacatatac atatactata catatacata tacatatact aagtatacgt atatacagta 120 catagtatat gtatactata tagtatgtat atatagcata tagtatgcgt atactctata 180 tagcatatag tatgcatata cgctatatag catatagtat gcatatacta tatatagtat 240 300 agtatgcgta tactatatat atagtataga gtatgcgtat actatatat tagtatagag 360 tatgcgtata ctatatatat agtatagagt atgcgtatac tatatatat gtatagagta 420 tgcgtatact atatatag tatagagtat gtatatatat agta 464

<210> 132

<211> 430

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(430)

<223> MAR of chromosome 2 genomic contig; 19647266..19647695 Seite 118

# **SEL PCT 012.ST25**

<400> 132 60 tataatatat aaactatata ttaatataat atatataaac tattatataa atacatatta 120 tatatttata ttatatataa cataattata tatattttca tattgtatat aataaagaaa 360 430

<210> 133

tatataatat

<211> 2131

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(2131)

<223> MAR of chromosome 2 genomic contig; 20481223..20483353

<400> 133

tatatataaa tatatttata tttaatatat atttatataa atatatttt atataaatat 60 atatttaata taaatatott tatatttaat atatatttaa tataaatato tttatattta 120 atatatattt atatataaat atatatttat atttaatata tattaatatt taatatacgt 180 240

Seite 119

#### SEL PCT 012.ST25

300 tatatttata tttaatatat ttacatataa atatatttat atgtaatata tttacatata aatatattta tatttaatat atatgcatat gtaaatatat ttatatttaa taatatttat 360 420 atataaatat atttatattt aataatattt atatataaat atatttatat ttaatatata 480 ttaaatatat atttatattt aatatatat aatatttaat atatatttat atttaatata 540 tattatatat aaacatatat ttatatttaa tatatattat atataaacat atattatat ttaatatata ttatatataa acatatatti atatttaata tatattata tttaatatat 600 tatatataaa catatatta tatttaatat atatttatat taaatatata ttatatataa 660 720 acatatattt atatttaata tatatttata ttaaatatat atttatattt aatatatata 780 tattaaatat atatttatat ttaatatata tttatattaa atatatattt atattaaata 840 tatttatatt taatatatat ttatattaaa tatatattaa atatttaata tatatttata tttaatatat acatatatat ttatatttaa tatatacata tatatttata tttaatatat 900 acatatatat ttatatttaa tatatacata tatatttata tttaatatat aaatttatat 960 tttatatata taaaaatata tatttatatt taatatatat aaatatatat ttatatttaa 1020 tatatatatt tatattgaat atatacataa atatatattt atatttaata tataaacata 1080 tatttatatt tatatattaa atatatattt atatttaata tataaatata tatttatatt 1140 tatttaatat atttatgtgt attaatatat ttatatttaa tatatttata tattaatata 1260 tttatatttt atatttatat attaatatat ttatatttta tatttatatt ttatatattt 1320 tatttatata ttaataaatt tatattttat acagttatat aaatatattt atattttata 1440 cagttatata aatatattta tattttatag ttatataaat atatttatat tttatacagt 1500 tatataaata tatttatatt ttatacagtt atataaatat atttatattt tatacagtta 1560 tataaatata tttatatttt atacagttat ataaatatat ttatatttta tacagttata 1620 taaatatatt tatattttat acagttatat aaatatattt atattttata cagttatata 1680 aatatattta tatttatac agttatataa atatatttat attttataca gttatataaa 1740

#### **SEL PCT 012.ST25**

<210> 134

<211> 842

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(842)

<223> MAR of chromosome 2 genomic contig; 20483478..20484319

<400> 134

#### **SEL PCT 012.ST25**

<210> 135

<211> 645

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(645)

<223> MAR of chromosome 2 genomic contig; 20897566..20898210

<400> 135

#### **SEL PCT 012.ST25**

tatgtatgta tatatacaca tatatattta tattatatat gtatattata tacatatatt 420
tatattatat atgtatatat atttatcata tttatatgta atatgcatgt gtaataaata 480
atatacacat ttatatatgt atattatata catatattta tattgtatat gtatatatat 540
ttatatatat ttgtatatca tatatttata tattgtatat ttatgtatat tatatattta 600
tatattatat atgtattata taatatatat gtaaatatat attat

<210> 136

<211> 722

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(722)

<223> MAR of chromosome 2 genomic contig; 21664541..21665262

<400> 136

tataatatat attatattct atataatatg taaaatatat attatattct atataatgta 60 ttatatatag aatataatat attotatgta ttotataatc tatataatac atattatata 120 ttatatagaa tattataaat aatatattot atattatata tagaatatat totatatgtt 180 tatattctat atattatata tgaaatagta tataaaatat atataatata tataaaatat 240 gatatataat atatataaaa taatatataa tgtataatat ataaaataat atataatgta 300 taatatataa aataatatat aatgtataat atataaaata atatataatg tatattatat 360 420 aaaataatat ataatgtata ttatatataa aataatatat aatgtatatt atatataaaa 480 540

#### **SEL PCT 012.ST25**

<210> 137

<211> 305

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(305)

<223> MAR of chromosome 2 genomic contig; 22834991..22835295

<400> 137

<210> 138

<211> 352

<212> DNA

<213> Homo sapiens

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#### **SEL PCT 012.ST25**

<220>

<221> misc binding

<222> (1)..(352)

<223> MAR of chromosome 2 genomic contig; 25277762..25278113

<400> 138

<210> 139

<211> 342

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(342)

<223> MAR of chromosome 2 genomic contig; 25378452...25378793

<400> 139

tatgtacata tatatttat atattatata taatatata tatatgatat atataatata 60

#### **SEL PCT 012.ST25**

<210> 140

<211> 663

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(663)

<223> MAR of chromosome 2 genomic contig; 30209437..30210099

<400> 140

60 attgtataat agtaatatat agtatatgat atactatata ttacttatca tatatacaat 120 atatatata togtatattg tatattatat attgtatata tgtaatatat gatatgtaca 180 tatgttatat atgtatataa tatactatat tatatattgt atattatata catatataac 240 actattatac aatatataat atagcatatt atatacaata tagcatatac aatatataat 300 atagcatatt atatataata tagtatatta tatacaatat ataatatagc atattatata 360 taatataata tagtatatta tatacaatat ataatatagc atatacaata tagtatacaa 420 tatataatat agcatataca atatagtata ttatatataa tatataatat agcatgtaca 480 atatagtatg ttatatacaa tatataatat agcatataca atatagtata ttatatacaa 540

#### **SEL PCT 012.ST25**

tatataatat agcatataca atatatata ttatatacaa tatataatat agcatataca 600 atatagtata ttatatacaa tatataatac agcatataca atatagtata ttacatacag 660 tat 663

<210> 141

<211> 1200

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(1200)

<223> MAR of chromosome 2 genomic contig; 31725089..31726288

<400> 141

tgtacttata tattataatg tatatataaa gtatatactt tatatatact tatatattat 60 aatgtatatt attgtatata agtatatatc ataatatata cttacatatg ctcacatata ttataatgta tattgtatat attatataca tattatatat gtataatgta tatatacatt 180 atatatgtat aatgtatata tacattatat atgtataatg tatatataca ttatatatgt ataatgtata taatatatac aatatatgta taatatataa tatatacaat atatgtataa 300 360 tagtatatta tatattatat atgtatagta tataatatgt ataatgtata tattataata 420 480 540 tatatataat ataaataata tttattatat attaatataa atatttatat taatatata 600 ttattatata taaataatat ctatgatata aataatatat aatatacatg tatatgttat 660

## **SEL PCT 012.ST25**

aatatataca tataatatac atgtgtatat atactataca tgtatatata acatgtatat 720 atatacatgt atatatatta tgtatacatg tatagtatat atacatgtat atatatacat 780 840 acatgtatat atacacatat atactataca tgtatatata catgtatata tatacatgta 900 tgttatatac attattataa tatacatata tagtatacat tatatacatt atataatatg 960 cattattata atataatata cattattata atatacatta ttataatata atatacatta 1020 ttataatata cattattata atatacatta taataatata cattattata atatacatta 1080 taatattgaa gtatatatac tataatatat gtatatatta taatgtatat aatatacatt 1140 attatatata agtatgtatt atatataagt atatattata atatatgtat atacatatat 1200

<210> 142

<211> 325

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(325)

<223> MAR of chromosome 2 genomic contig; 32147252..32147576

<400> 142

#### **SEL PCT 012.ST25**

aatatataat atatttatat ataac

325

<210> 143

<211> 507

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(507)

<223> MAR of chromosome 2 genomic contig; 32312662..32313168

<400> 143

<210> 144

<211> 339

<212> DNA

<213> Homo sapiens

taatataaat attatattta tatttat

Seite 129

## **SEL PCT 012.ST25**

<220>

<221> misc binding

<222> (1)..(339)

<223> MAR of chromosome 2 genomic contig; 33651118..33651456

<400> 144

<210> 145

<211> 461

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(461)

<223> MAR of chromosome 2 genomic contig; 45073053..45073513

<400> 145

tgtgtataca tatatacgtg tacatataca tatatacatg tgtatatata tacgtgtaca 60

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#### **SEL PCT 012.ST25**

tatacatata tacatgtgta tatatatgta catatacata tatacatgtg tatacataca 120
tatatacatg tacatataca tatatacatg tgtatacata catatataca tgtacatata 180
catatataca tgtgtatact tacatatata catgtacata tacatatata catgtgtata 240
tatacatata tacacgtaca tatacatata tacatgtaca tatatacatg tatacatata 300
tacatgtaca tatgtacata tatacatgta tacatatata catgtacata tgtacatata 360
tacatgtata catatataca tgtacatatg tacatatata catgtataca tatatacata 420
tgtacatacg cacagataga catatataca tatgtacata c

<210> 146

<211> 1162

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1162)

<223> MAR of chromosome 2 genomic contig; 45487691..45488852

<400> 146

#### **SEL PCT 012.ST25**

480 540 atattatata taatatctat tatatctatt atatattata tatataatat ctattatatc 600 tattatatat tatatata atatctatta tatctattat atctattata tatatatcta 660 ttatatctat tatatatt atatacataa tatctattat atctattata tatattatat 720 780 tatatgtact atctattata tctattatat ctattatata tatactatct attatatcta 840 ttatatatat tatatata ctatctatta tatctattat atatattata tatatactat 900 ctattatata tctattatat atattatttt atattatata tagtatctat tacatatatt 960 atattatatt atatataata totattatat atattatatt atattataaa taatatatat 1020 ataattaata taatatgtaa ta 1162

<210> 147

<211> 562

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(562)

<223> MAR of chromosome 2 genomic contig; 45516233..45516794

<400> 147

#### **SEL PCT 012.ST25**

120 atatacatat tatatatat atatatacat attatatatt atatataata tatacatatt 180 240 ttatatata atattatata tottatatat aaatataata tataatatat ataatatta 300 360 420 tatattatat aaatatata aaatatataa aatatataaa tatgtaaaat ttatatttat 480 540 tacataatat atactatata ta 562

<210> 148

<211> 801

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(801)

<223> MAR of chromosome 2 genomic contig; 45727251..45728051

<400> 148

#### **SEL PCT 012.ST25**

360 420 480 540 600 660 720 780 atatatatat atatatagaa t 801

<210> 149

<211> 346

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(346)

<223> MAR of chromosome 2 genomic contig; 50937238..50937583

<400> 149

#### **SEL PCT 012.ST25**

# taaaatatat attatattat ataaaatata tattatacta tatata 346

<210> 150

<211> 462

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(462)

<223> MAR of chromosome 2 genomic contig; 55672627..55673088

<400> 150

60 120 tattataat atatatcata taaataatat atatttataa tagatatcat ataaataata 180 tatatttata atagatatca tataaataat atatatttat aatagatatc atataaataa 240 tatatattta taatagatat catataaata atatatattt ataatatata tcatataaat 300 360 ataatatata tttataatag atatcatata aataatatat atttataata gatatcatat 420 aaataatata tatttataat agatatcata taaataatat at 462

<210> 151

<211> 401

<212> DNA

<213> Homo sapiens

#### **SEL PCT 012.ST25**

401

<220>

<221> misc\_binding

<222> (1)..(401)

<223> MAR of chromosome 2 genomic contig; 56081352..56081752

<400> 151

tatacatgta tgtattcgta tatgtatgtt atatatgtat atgtgttata tacatataca 60
tatatacatg tatatgtgtt atatacatat acatatatac atgtatatgt gttatataca 120
tatacatata tacatgtata tgtgttatat acatatacat atatacatgt atatgtgtta 180
tatacatgtg tatgtgtata tgtatatata catatatgtg tatgtgcatg tgtatatata 240
catatatgta tatgtgtata tgtatatata catatatgta tatgtgtatg tgtatacgta 300
tatatacata tatgtgtatg tgtatgtgta tacgtatata tatacatata tgtgtatgtg 360

<210> 152

<211> 765

<212> DNA

<213> Homo sapiens

tatacgtaca tatacatata tgtgtatgtg tatacgtaca t

<220>

<221> misc binding

<222> (1)..(765)

<223> MAR of chromosome 2 genomic contig; 56404208..56404972

<400> 152

#### **SEL PCT 012.ST25**

120 tatattatat aatatataa gaatatatat tatatattat ataaagaata tatattatat 180 ataatatata aagaatatat aatatataat atataaagaa tatatattat atataatata 240 taaagaatat atattatata taatatataa agaatatata ttatatatta tataaagaat 300 acatatatat aatatataa gaatatatat tatatataat atataaagaa tatatattat 360 420 tatataaaga atatatata tatataatat ataaagaata tatattatat atattatata 480 aagaatatta tatattatat aaagaatata tattatatat aatatataaa gaataaacat 540 atatactata tataaagaat atacattata tatactatat ataaagaata tacattatat 600 atactatata taaagaatat atataatata taaagaatat acattatata taatatataa 660 agaatatatt atatattata taaagaatac attataatat aaagaataca ttatatataa 720 tataaagaat acattataat atataaagaa tatatataat atata 765

<210> 153

<211> 443

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(443)

<223> MAR of chromosome 2 genomic contig; 61953416..61953858

<400> 153

tttatatatt atagataaaa ttatattata ttacatgtaa tatataatat gtaaaatata 60 ttatattaca tatataatat ataatatgta aaatatatta tattacatat ataatatata 120

#### **SEL PCT 012.ST25**

atatgtaaaa tatattatat tacatatata atataaaata ttacatataa tatattttac 180 ataaatatat attatctatt acatattat tatatgtaat aatatgtaca tatgtataaa 240 tatgtatata tttatacata tgtatatatt atatatacat atatatgtat atattatata 300 tacatatata tgtatatatt atattatata tacatatata tgtatatatt atattatata 360 tacatatata tgtatatatt atattatata tacatatata tgtatatata ttataaatat 420 gtataataaa gatttatatg taa 443

<210> 154

<211> 372

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(372)

<223> MAR of chromosome 2 genomic contig; 62076211..62076582

<400> 154

<210> 155

#### **SEL PCT 012.ST25**

<211> 484

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(484)

<223> MAR of chromosome 2 genomic contig; 62158581..62159064

<210> 156

tcat

<211> 644

<212> DNA

<213> Homo sapiens

<220>

#### **SEL PCT 012.ST25**

<221> misc\_binding

<222> (1)..(644)

<223> MAR of chromosome 2 genomic contig; 68145036..68145679

<400> 156 tatatatatg ctaatatatg taatatatat tatatatatg ctaatatata tatgctaata 60 120 atataaatat ataatataaa tatatataat atatactata ttatatatta tgtataacat 180 240 taatataaca atatattta tatattatat gttatatatt atatattata tataatataa 300 cataatatat aatatatat atattatata ttacatatat tagcaatatt atatataaaa tatatataat atatataaaa tatataaaa aatataaaat atatatcaaa atataaacta 420 tataatatat aaaaatatat tatatataat atataaaaat ataaactata taatatataa 480 tataatatat aaaaatatat ataaaatata aaaaatatat ataaaatata aaaaatatat aaaataatat aaaatatata atataata atataatata taat

644

<210> 157

<211> 530

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(530)

<223> MAR of chromosome 2 genomic contig; 71257289..71257818 Seite 140

# **SEL PCT 012.ST25**

<400> 157 60 atatctatta tatttatata ctttatataa attatatcta ttatatttat atactttata taaattatat ctattatatt tatatacttt atataaatta tatctattat atttatatac 120 tttatataaa ttatatctat tatatttata tactttatat aaattatatc tattatattt atatacttta tataaatata taattatatt tatatacttt atataaatat aattataaat 240 atatttatat actttatata aatataatta taaatatatt tatatacttt atataaatat 300 aattataaat atatttatat actttatata aatataatta taaatatatt tatatacttt 360 ataattatat gttatattta taattatatt tatataattc ataattatat acattatgtt tatagttata taatttataa ttatatacat tatatttata tttatataat ttataattat 480 ataaattata taaattatat aaattatctt taatttatat tatataatct 530

<210> 158

<211> 337

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(337)

<223> MAR of chromosome 2 genomic contig; 73413615..73413951

<400> 158

acttatatta tatataacta tattattgta tattaatata aattaatgat atataatata 60 ttaattatat attattatat gtgatataaa atacttatat ttatactgta tatatgtata 120 tacacacata tatgtatata tgtatatata cacatatgta tatatgtata tgtatatatg 180

#### **SEL PCT 012.ST25**

tatactgtat atatgtatat acacacatat atgtatatat gtatatgtat atatgtatac 240 tgtatatatg tatatacata tatacatata tgatatatat cacatatatg tgatatataa 300 atatatttat ataaatataa tattaatatt tatatta 337

<210> 159

<211> 1340

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1340)

<223> MAR of chromosome 2 genomic contig; 77011049..77012388

<400> 159

atgtatttta tatagtatat attatgtatt atattgatat aattatataa caattattta 60 120 180 ataattcata tatatttata tattaaataa ttcatatat tttaaataat taatacatat 240 300 ttatagatta aattaatata tattatata ttaaattaaa tttaatatat tatatatta 360 tataatttaa atttaataat ttatataatt taatttaatt taatataatt aaaatatatt 420 480 540 tatatttaat atataatata tatttaatat ataatatat taatatata tatatatta 600 660

#### **SEL PCT 012.ST25**

720 780 840 900 atatttaata tataatatat atttgatgta taatatattt aatatataat atatatttga tgtataatat atttaatata taatatatat ttgatgtata atatatttaa tatataatat 960 1020 1080 tataatatat atttgatata taatatattt aatatataat atatatttga tatatattta tatatttaat atataatata tatttgatat ataatatatt taatatataa tatatatttg 1200 atatataata tatttaatat ataatatata titgatatat aatatattta atataaata 1260 tatatttgat atataatata ttttcttatt aattatttat atataatata taaatatata 1320 1340 ttaattaatt atatattaaa

<210> 160

<211> 937

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(937)

<223> MAR of chromosome 2 genomic contig; 78226855..78227791

<400> 160

Seite 143

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#### **SEL PCT 012.ST25**

180 tatatatgtg tatatatgtg tatatataca tatatgtgta tatatgtgta tatatacata 240 tgtgtatata tgtgtatata tacatatatg tgtatatatg tgtatatata catatatgtg 300 tatatatoto tatatataca tatatotota tatatotota tatatotota tatatoto tatgtgtata tatgtgtata tatacatata tgtgtatata tgtgtatata tacatatatg 360 420 tgtatatatg tgtatatgtg tgtatatata catatatgtg tatatacaca catatatgtg 480 tatatatoto tatataca tatatotata tatacatata tototata tototata 540 tacatatatg tgtatatatg tgtatatata catatatgtg tatacataca tatatgtgta 600 tatatotota tatatacata tatototata catacatata tototata tatotota 660 tacatatatg tgtatacata catatatgtg tgtatatgtg tatacataca tatatgtgtg 720 tatatatgtg tatacatatg tgtgtatatg tgtatatata catatatgtg tgtatatatg tgtatatata catatatgtg tgtatatatg tgtatatata catatatgtg tgtatatatg 780 840 totatatata catatatoto totatatato totatatata catatatoto totatatato 900 tgtatatata catatatgtg tgtatatatg tgtatatata catatatgtg tgtatatatg 937 tgtatatata catatatgtg tgtatatatg tgtatat

<210> 161

<211> 1350

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1350)

<223> MAR of chromosome 2 genomic contig; 79287748..79289097

<400> 161

# SEL PCT 012.ST25

tatatatatt atatatag taactgttct attatatata tattatatat atttctgttc 60	
tattatatat tatatatat atattatata ttatatgtaa tatattatat atattataag 120	)
taatatatta tatatattat atgtaatata ttatatata	0
tattatatgc aatatgttat atatattata tgcaatatgt tatatatatt atatgcaata 2	40
tattatatat attatatgca atatattata tataatatat gtaatatatt atattatata 30	0
ttatatgtaa tatcttatat attatatgta atatattata tatattatat	I
atatatata tatgtaatat attatatatt atatgtaata tattatctta tatatattat 420	١
atgtaatata ttatattata tattatatgt aatatatat	0
tatatgtaat atatattata tgtaatatat tacatattat atgtaatata tattatatgt 54	0
aatatattac atattatatg taatatatta catattatat gtaatatatt atatgtatta 60	00
tatgtaatat attatatgta ttatatgtaa tatattatat gtattatatg tattatatgt 660	
aatatattat atgtattata tgtaatatat tatatattat atgtaattat attatatgta 720	)
atatattata ttatatatta tatatattat atgtaatata ttatattata tattatatat 780	
attatatgta atatattata ttatatatta tatatattat atgtaatata ttatattata 840	
tattatatat attatatgta atatattata ttatatatta tatatattat atgtaatata 900	
ttatattata tattatatat attatatgta atatattata ttatatatta tatatattat 960	
atgtaatata ttatattata tattatatat attatatgta atatattata ttatatatta 1020	)
tatatattat atgtaatata ttatattata tattatatat attatatgta atatattata 1080	)
ttatatatta tatatattat atgtaatata ttatattata tattatatat attatatgta 1140	
atatattata ttatatatta tatatattat atgtaatata ttttatatta tatatattat 1200	
attatatatt atatgtaata tattatatta tttattatat attatatatt atatgtaata 1260	
tattatatta tttattatat atattatatt atttatta	
atattatatt atatatattt ctgttctaat 1350	

<210> 162

<211> 332

#### **SEL PCT 012.ST25**

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_difference

<222> (1)..(332)

<223> MAR of chromosome 2 genomic contig; 81142998..81143329

<400> 162

ctatgtatat aactatatat aactattata taacttaata agatatataa ctattatata 60 acttaataag ttatatataa ctattatata taacttaata agttatatat aactattata 120 taacttaata agttatatat aactattata taacttatata agttatatat aactatatat 180 aacttaataa gttatatata actattatat aacttaataa gttatatata actattatat 240 aacttaataa gttatatata actattatat aacttaataa gttatatata actatatata 300 acttatatac aacttattaa gctatatata ta 332

<210> 163

<211> 327

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(327)

<223> MAR of chromosome 2 genomic contig; 84019536..84019862

#### **SEL PCT 012.ST25**

<400> 163
actgacagta tacatactgt atatatatac agtatgtata catatacagt atgtatacta 60
tatacagtat gtatactgta tatatatata cagtatgtat actgtatata tatacagtat 120
gtatacgtat gtatactgta tatatgtatt atagtgtata tatgtattat agtgtatata 180
tgtattatat atattatagt gtatgtatta tatgtgtata tacatataat atattataca 240
tatacatatg cacaatatgt atatgtatta tatgtattca tatacatata tgtatatgta 300
taatatatgt atacatataa tacacat 327

<210> 164

<211> 407

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(407)

<223> MAR of chromosome 2 genomic contig; 1448030.,1448436

<400> 164

#### **SEL PCT 012.ST25**

<210> 165

<211> 1959

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1959)

<223> MAR of chromosome 2 genomic contig; 2117630..2119588

<400> 165

tatacatgtt atagtgtata tagtatacta atatataatg tatgtatgtg tatacatata 60 cacatataat atacacatat ataatatata tagtatataa taatgtataa tatataatat 120 ataatataaa atgtatagta tactacatat ttatatatag tatatagtat gcatagtaca 180 tatatactat atatgtagta tactatagtg tatatatagt acaccatata tagtataaat 240 atactatata gtatatgtac tatatatata ctatatagta tatacagtat acatatatag 300 tatacctata ctatatagta tatatagtgt gcgtatacta tatagtatat atagtgtgcg 360 tatactatat agtatatata gtgtgcgtat actatatagt atatatagtg tgcgtatact 420 atatagtata tatagtgtgc gtatactata tagtatatat agtatacata tatagtgtgc 480 gtatactata tagtatatat agtatacata tatagtatgc gtatactata tatagtatac 540 atatatagta tatctagagt atatgtagta tgtatagtat atatagtcta catactgtat 600 atacagtata tatatactet atagtataet atacagtata gtataetata tagtataeaa 660 tatatgtata ctatagaaac acactatata tagtatacta tatatactat atactatata 720 ctatatatag tatactatat atactacata ctatatatag tgtatgtata gtatatataa 780 

#### **SEL PCT 012.ST25**

900 attatata ataatataat tatatattat aaaatatata ttittatatt atatattitt 960 atataaatat ataatatta tatagtataa tatataatat gttatatagt 1140 atcttatact attatactat atattata tagtgtatat atagtatact atatatagtg 1200 tatatagtgt atactatagt gtatatagtg tatactatag tgtatatagt gtatactata 1260 tacactgtat atagtagtgt atactatata cactgtatat agtagtgtat actatataca 1320 ctgtatatag tagtgtatac tatatacact gtatatagta gtgtatacta tatacactgt 1380 atatagtagt gtatactata tacactgtat atagtagtgt atactatata cactgtatat 1440 agtagtgtat actatataca ctgtatatag tagtgtatac tatatacact gtatatagta 1500 gtgtatacta tatacactgt atatatagta tattatatat actatatatg tatatatagt 1560 atacatatat attatatata cagtatatat agtatatata ctatgtagta tatatagtat 1620 atatactata tagtatgtat agtatactat atagtatata tagtatata tatagtatat 1680 atactatata gtatatatag tatattgtat atatagtata tatactatat agtatatata 1740 gtatattgta tatatagtat attgtatata tagtatacat agtatgtata tatagtatat 1800 atagtataca tatatagtat gtacacagta tatatagtct atatgtatac tacatatagt 1860 atacatgtat actatactac atatagtata catgtatact atactacata tagtatacat 1920 gtatagtata ctacatatac tatacatgta tagaatact 1959

<210> 166

<211> 520

<212> DNA

<213> Homo sapiens

<220>

# **SEL PCT 012.ST25**

<221> misc\_binding

<222> (1)..(520)

<223> MAR of chromosome 2 genomic contig; 2119984..2120503

<400> 166
tatgtatgca tegtatacat atatagtata tatatgtatg categtatac atatatacag 60
tatatatatagt atgcategta tacatacagt atactatata tacagtatat acagtatact 120
atatatacag tatatacagt atactatata tacagtatat acagtatact gtatatacag 180
tatatacagt atatatagta tactatatat acagtatata tactatgtat tetatatata 240
gtatagtgta catagtatac atatagtata cactatacta tatatagtat actatatata 300
ctetatatag tatatatagt atactatata tagtatatat gtatactata tatagtgtat 360
atatatacta tatatagtgt atatatatac tatatatagt atatatatac actatatat 420
gtatagtata gtgtatatat agtatagtat atgtatatat acacatgtat acatgtatat 480

<210> 167

<211> 954

<212> DNA

<213> Homo sapiens

atgtatacta atatatacta atatatgtat aaatatatat

<220>

<221> misc binding

<222> (1)..(954)

<223> MAR of chromosome 2 genomic contig; 2578285..2579238

<400> 167

# **SEL PCT 012.ST25**

tattatatat aacittataa tatataatat atattatata taacittata atatataata	60
tatattatat ataactttat aatatataat atatattata tataacttta taatatataa	120
tatatattat atataacttt ataatatata atatatat	180
aatatatatt atatataact ttataatata taatatata tatatata	240
ataatatata ttatatataa ctttataata tataatatat attatatata	300
atataatata tattatatat aactttataa tatataatat atattatata taactttata	360
atatataata tatattatat actatatata atatataact ttataatata taatatata	420
tatatactat atataacttt ataatatata atatatat	480
aatatataat atatattata tataacttta taatatataa tgtatattat atattatata	540
ttatatatta tatataactt tataatatat aatgtatatt atatattata tataacttta	600
taatatataa tatataatat aatatataac tttataatat atatatcata tattatatat	660
aactttataa tatatatcat atattatata taactataat atatatat	720
ataactataa tatatatatc atatattata tataacttta taatatatat	780
atatataact ttataatata tatcatatat tatatata	840
ttatatataa ctttataata tatattatat ataactttat aatatatat	900
tataacttta taatatatat catatattat atataacttt ataatatata tcat	954

<210> 168

<211> 452

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(452)

<223> MAR of chromosome 2 genomic contig; 3836217..3836668 Seite 151

452

#### **SEL PCT 012.ST25**

<210> 169

<211> 417

<212> DNA

<213> Homo sapiens

acatgtaatt atatgaatat atatttatac at

<220>

<221> misc binding

<222> (1)..(417)

<223> MAR of chromosome 2 genomic contig; 3837666..3838082

<400> 169

gatatatata tttatataaa tatatatata aagagatata tttatatatt tatttatata 60 aatatattto tttatataaa gatatatgta aatatattta tttatataaa tatatttata 120 tatgtaaata tatatttata tattatata tttatatat tatttatata aatatatata 180 tttatatatt tatttatata tataaaaata tataaatata aatatatata 240

# **SEL PCT 012.ST25**

attataaata tagaaataaa tataaatata aatatataaa tataaatata 300 tataaatata aatatatata aatataaata tataaatata taaaatata taaaatata taaatata aaaatatata taaatata taaa

<210> 170

<211> 1197

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1197)

<223> MAR of chromosome 2 genomic contig; 6294846..6296042

<400> 170

tatatactaa tatgtatata taaatatata aatatatata cacgtgtata tataaatata 60 120 tatgtatata taaatatata tacatatatg tatataaaaa tatatacgta tatacgtata tacgtatata tagatatata cgtatatacg tatatacgta tatatagata tatacgtata 180 tacgtatata tagatatata cgtatatacg tatatacgta tacatgtgta tatacgtata 240 tacacatata cgtatacatg tgtatatacg tatatgtata cattatatat acgtatatat 300 acatatatgt atacatgtat atataaatat atacatatat gtatatatta tacatatatg 360 420 taatatatat attatatata atatattata tattatata aatatataca tatataatat 480 540 tatatataat atatgtatat tatatataca tatgtatata tgtacatatt atatatgtat 600 atatgtacct attatatata catatgtata tatgtaccta ttatatatac atatgtatat 660

# **SEL PCT 012.ST25**

atgtacatat tatatataca tatgtatata tgtacatatt atatacat atgtatatat 720 gtgcatgcat atataatata taatatata tagattataa tattatatac atatcatata 780 ttatatactt atatatacat gtatatatta tatacatatt atatattata tacatataat 840 atatgtatat aatatataca tatattatat attatatat atacattatg ttatatatta 900 tgttatataa tatatatat ataatataca tatattatat ataatatata catatataat 960 aaataatata taattatata tataatatat gcatataaat atgtaatata ttttatatta 1020 tatatgatca tatataatat gacatattat atatgattat atatatgata tattatatat 1080 gattatatat attatata aatatatgat tatatataat catatatata aatatatgat 1140 1197

<210> 171

<211> 362

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(362)

<223> MAR of chromosome 2 genomic contig; 6506971..6507332

<400> 171

tatatatagt gtatactata tatacgctat atgcacacat aaactatata tacagtatat 60
aatatgcgta tactatatac acagtatata ctacatgtat actatatata gtatataaga 120
tatatactat gtatataata tatatactag gtatatatat ccatatatat actatatact 180
atagtatata catatatatg tacgtatata tgtatatgta catatatatg tagtatgtat 240
atatatacat atatacacac tatagtatat acatatatat actatatata ccctatatag 300

# **SEL PCT 012.ST25**

agtatattat atacagtata ctatatatac tatatatacc ctatatagag catgtctatg 360

ct 362

<210> 172

<211> 2578

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(2578)

<223> MAR of chromosome 2 genomic contig; 6507395..6509972

<400> 172

ggtatactat atatactata gagtatactt tatagtatat atacctatat tatatatata 60 tacatacact gtatagtata tatggtatat atactatata tggcatatat agtttatata 120 180 tatactatat atggtatata tagtttatat atatactata tatggtatat atagtttata tataccatat atggtatata tagtttatat agtacatata gtatatatac acactgtata 240 gtatatatta tgtagtatat atactatata tactgtatat atagtataaa tactatatat 300 agtatacact atatactata cactatatat actatatact atatactata tatagtatac 360 420 tatatagtat atagtatact ctatatgtac tatagagtat actatatata ctatacataa aatatttta tatatagtac agcgtatact atatactata tatagtatac tctatatgta 480 540 ctatagagtg tagtatatac tatacagtat actctatata tactatacag tacactatat atactatata tagtatattt tatatatagt acagtatata cagtatatat attatactat 600 660 atgtagtaca tatatagttt agtatatata gtatatatac tatactatat gtactacata 720 tataatagta tatatagtat atatactata ctatatgtag tacatatata gtttagtata

# **SEL PCT 012.ST25**

780 catatatagt atatatgcta tatatactat atagcatata ctatatacta tatatacagt 840 atatatagca tatatagcat atataatata tatacttttg atatacatac tatatacagt 900 atatatagta tatatactgt ataaatatac tatatatacc gtatatgcac actatatgct 960 atatatacta tatacactat atacagtata tatagtacac tatactatat aaagtatata 1020 tagtatacag tacactatac tatatacatt atatatagta tatattatac atagtatata 1080 gtatataaat agtatatata gtatatacag tatatatata gcatacttta tatagtatac 1140 acagtatata gatactatat atgctatata tagtatctat atactgtata ttatatatac 1200 taatatagta tatatgtata tatatactgt atatataata tatacatata tagtatatat 1260 actatacata cacactatac atatgtatat atactataca tactatatac tatatacct 1320 atatatacta tatagtatat tatatatcct atatatacta tatagtatat tatatatcct 1380 atatatacta tatagtatat tatatatact atataccata tatactatat atactgtata 1440 gtatactata tatactatat agtatactgt atatactata tagtatactg tatatactat 1500 atagtatact gtatatacta tatagtatac tgtatatact atatagtata ctgtatatac tatatagtat actgtatata ctatatatac tatatagtat actgtatata ctatatagta 1620 tactatatat actatatacc atatatacta tgtatatact atatatagta tatactatgt 1680 atatgctata tatagtatat atagtatata tgctatatat agtatatata gtatatatgc 1740 tatatataca gtctatatat agtatatata ctatatagac tatatatata gcatatatac 1800 tatatatact atatataata tatatggtat atacatagta totatatgta gtatotatat 1860 atagtaccta tatatactat atataggtac tatatatagt atatatactt tatatagata 1920 ctatatatag tatatatact ttatatagta tatatagtat atgtagcata tatagtatat 1980 atagtatata tagtatatag tatgtatagt atatatagat tatattgtat atacagtata 2040 tatactgtat atactatata aatagtacat acagtatata cagtatatat gtactatata 2100 tagtatatac agtatataca gtatatatgt accatatata gtatatacag tatatacagt 2160 atatatgcac tatatgttat atacagtata tacagtatat atgtactata taaatagaat 2220

# **SEL PCT 012.ST25**

atactctata tacagtatat atgtactata taaatatata cactatgtac agtatatatg 2280 tactatataa atagtatata cactatatac agtatatatg tactatatag tgtatacagt 2340 atatacagta tataggtact atatatggta tatacagtat atatgcacta tatggtatat 2400 acagtatata tgcactatat atggtatata cagtatatat gtactatata tggtatatac 2460 agtatatatg tactatatat ggtatataca gtatatatgt actatatatg gtatatacag 2520 tttatacagt atatatgcac tatatatggt atatacagta tacatgtact atatatgg 2578

<210> 173

<211> 598

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(598)

<223> MAR of chromosome 2 genomic contig; 7770400..7770997

<400> 173

gtgtattgta tatacatata cgtatctacg tatatacata tatgtattgt atatacatat 60 atgtattgta tatacatata tgtatatacg tatatacata tatgtattgt atatacatat 120 atgtatatac gtatatacat atatgtatat acgtatatag atatacatat atatgtattg 180 tatatacata tatgtatata catatataca tatatattga tatacatata tatgtattgt 240 atatacatat acaatatatg tatatataca tatacatata caatatatgt atatacatat 300 atatgtattg tatatacata tatatgtatt gtatatacat atattgatat acatatatgt 360 atatatacat atatgcatat atgtatatat acatatatgc atatatgtat atatacatat 420 atacatatgt acatatatac atatatacat atatgtatat atacatatat acatatgtac 480

# **SEL PCT 012.ST25**

atatatacat atatacatat gtacatatat acatatatac atatgtacat atatacatat 540 atagatatat atacacatat atagatatac ttatatgtat atatacatac atacatat 598

<210> 174

<211> 1048

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(1048)

<223> MAR of chromosome 2 genomic contig; 8332422..8333469

<400> 174

60 120 acatatata aatataacat atattatata taacatatat aaaatataac atatattata 180 tataacatgt ataaaatata acatatatta tatataacat gtataaaata taacatatat 240 tatataacat gtataaacta taacatatat tatatataaa atatattata tgttatatat 300 tataaataaa atatattata tgttatatat tataacatat tatataaata atatataata 360 420 catatattat ataacatata acatataaca tatattatat ataacatata acatataaca 480 tatattatat ataacatata acatataaca tatattatat ataacatata acatatata 540 atatataaca tataacatat attatattat atataacata taacatatat tatattatat 660 720

#### **SEL PCT 012.ST25**

<210> 175

<211> 375

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(375)

<223> MAR of chromosome 2 genomic contig; 8909678..8910052

<400> 175

tatatacaca tatatacgta tgaatatata tacacatata cgtatgaata tatataccca 60
tatacgtatg aatatacaca tatatatacg tacgtatata tatacacata tatacgtacg 120
tatatatata cacatatata cgtacgtata tatatacaca tatatacgta cgaatatata 180
tacacatata tacgtacgaa tatatataca catatatacg tacgaatata tatacacata 240
tatacgtacg aatatatata cacatatata cgtacgaata tatatacaca tatatacgta 300
cgaatatata tacacatata tacgtacgaa tatatataca catatatacg tacgaatata 360
tatacacata tatac 375

<210> 176

# **SEL PCT 012.ST25**

<211> 563

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(563)

<223> MAR of chromosome 2 genomic contig; 10572503..10573065

<400> 176

atttataata tatatgtata aatatatgta tatatttata titaaatata tgtatatata 60 tttatattta aatatacgta tatatattta tatttaaata tacgtgtata tatttatatt 120 taaatatacg tgtatatatt tatatttaaa tatacgtgta tatatttata tttaaatata 180 240 cgtgtatata tttatattta aatatacgtg tatatattta tatttaaata tacgtgtata tatttatatt taaatatacg tgtatatatt tatatttaaa tatacgtgta tatttatatt 300 taaatatacg tgtatattta tatttaaata tatgtatgta tttataaata tatatttaaa 360 420 gtatatattt ataaatgtat acatgtatat ataaatatat atattttaaa tatatattta tatatatatt tatatattta tataagtata tatatattta aatatatgta tatatttata 480 tattatata agtatatata tttaaatata tgtatatatt tataatatat attttaaata 540 tatatttata tatttattat ata 563

<210> 177

<211> 595

<212> DNA

# **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(595)

<223> MAR of chromosome 2 genomic contig; 11609694..11610288

<400> 177

tataaatact atatatagta tatataatat tatatatact atatataaat atatgtagta 60 taaataatat ataatataga tatataatat aatataatat gitataaata taaatatat 120 tatataattt aatttataat atataatata taatatataa tttaatttta taatatataa 180 tatataattt aattttataa tatataatat ataatatgta aattatatat aatttaatat 240 atctaaatta tataatttaa atataaatat aatataaata tatctaacat aatatacata 300 acataaatat atatagtata tatagtacat ataaatatat atagtacata tagtatatat 360 420 480 tatatattat taaatataat aataatttat tatatatact atatattatt atgtattata 540 595

<210> 178

<211> 662

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(662)

<223> MAR of chromosome 2 genomic contig; 12699804..12700465
Seite 161

# **SEL PCT 012.ST25**

<400> 178 60 120 tatggtatat atatatggta tatatatatt tgctatatat atagcagatc tgctatatat 180 atatatttgc tatatatata gcagatctgc tatatatatt tgctatatat atgctatata 240 tatgctacat atatgctata tatatgctat atatatgcta tatatatgct atatatatgc 300 tatatatatg ctacatatat gctatatata tgctacatat atgctatata tatgctatat 360 atatatgcta tatatatgct atatatatat gctatatata tgctatatat atatgctata 420 tatatgctat atatatgc tatatatat ctatatat gctatatat tagcatatat 480 atatagctat atatatgcta tatatatagc ttatatatat gctatatatg ctatatatat 540 gctatatata tagctatata tatgctatat atagctatat atatgctaca tatatgctat 600 atatatgcca tatgtatgct atatatatgc tatatatat tgctatatat atgctatata 660 ta 662

<210> 179

<211> 649

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(649)

<223> MAR of chromosome 2 genomic contig; 12821904..12822552

<400> 179

# **SEL PCT 012.ST25**

tatgtaatat tatatata aattatatat tatacatatg taatattata tatataaa 60 ttatatatta tacatatgta atattatata tatataaatt atatattata catatgtaat 120 attatatata tataaattat atattataca tatgtaatat tatatatata taaattatat 180 attatacata tgtattatat atataaatta tatattatac atatataata tatataaa 240 300 aattatatat tatacatata taatatatat aaattatata ttatacatat ataatatata 360 taaattatat attatacata tataatatat ataaattata tattatacat atataatata 420 tataaattat atattataca tatataatat atataaatta tatattatac atatataata 480 tatataaatt atatattata catatataat atatataat tatatattat acatatataa 540 600 649

<210> 180

<211> 3191

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(3191)

<223> MAR of chromosome 2 genomic contig; 15356889..15360079

<400> 180

#### **SEL PCT 012.ST25**

atatattaca tattattata taatatatat tatataacat atataacata tactatatat tatataacat atataattgt atatgtatta tatatattat atatacttat acataatata 300 360 taaataatta aatatatott ataaatataa caaatatata acatatataa catatataac atatatata a ttacataaaa tatataatac ataatatata ttatgcaaca tattatataa 420 tatataacat ataatgtata ttatattata tcatatataa tacataatat ataatatatg 480 atataatata atatattata tatgatataa tataatatat tatatatgtt ataatataat 540 atatattata tataggatat attataacat attacatatg atataataaa ttttatctta 600 tatataggat atattataat atatcacata tagcatatat taaaatatat tacatatagt 660 atattatata tactatatgt atatatacat atagtatatt atagtatatt atacagtata 720 tattatatat actatatata gtagtataca gtatatatta tatatactat atatagtagt 780 atacagtata tattatacag tatatattat atacactata ttatatatta tgtataatat 840 atactatata tagtatatta tgtagtatat attaaacata atagatatat agtatatact 900 atagataata gatattatat agtatatagt atatattata tataatatat ataatatata 960 ttatatacat atatgatata tgatatatta tatataatat atataatata taatatatgt 1020 taataatata tattataa tataacatat ataaatataa taatatata tatatgatat 1140 aacatacata aatataataa catatataat atatattata tattatattg tatatatgat 1200 atactatata ttacacatta tacattattt ataatatata attaatatat aacatatatt 1260 agataacata taattatatc tgtaacatat ataagatata attacatata taacatatat 1320 aattatatat atatttatct aattatatat gaaattatat atgacatata aaattatata 1380 ttatatatgt tatatgtatt atatattata tatgttatat atgttatata taacatatat 1440 aacatatata acacacacat ataacatata taacatatat tacatatata acatatataa 1500 cacatatata attatctaac atagataata tatataatat ataatataac atatatatta 1560 tatattatac actotattat attatatata ttatacataa tatataatat atatgatata 1620 atataataca ttgtatatac gatataatat atattgtaca tagtataata tacatatata 1680

# **SEL PCT 012.ST25**

gtatattatg tataacataa tatatagtat attatgtata acataatata tagtatatta tgtataacat aatatatagt atattatgta taacataata tatagtatat tatgtataac 1800 ataatatata gtatattatg tataacataa tatatagtat attatgtata acataatata 1860 tagtatatta tgtataacat aatatatagt atattatgta taacataata tatagtatat 1920 tatgtataac ataatatata gtatattatg tataacataa tatatagtat attatgtata tataatatac atattatata gtatattatg tatatataat atacatatta tatagtatat 2040 tatgtatata taatatacat attatatagt atattatgta tatataatat acatattata 2100 tagtatatta tgtatatata atatacatat tatatagtat attatgtata tataatatac 2160 atattatata gtatattatg tatatataat atacatatta tatagtatat tatgtatata 2220 taatatacat attatatagt atattatgta tatataatat acatattata tagtatatta 2280 tgtatatata atatacatat tatatagtat attatgtata tataatatac atattatata 2340 gtatattatg tatatataat atacatgtta tgtagtatat tatgtatata taatatacat 2400 gttatgtagt atattatgta tatataatat acatgttatg tagtatatta tgtatatata 2460 atatatata ggtgtatata tattatgtat atataatata taaggtatat atattatgta 2520 tgtatatata atatgtatat tatatataat atatattatt tatatacatt atgtatctat 2640 ataatatata ttatgtatat attaggtatc tatataatat atattatgta tatatattat 2700 gtatctatat aatatatat ttatgtatat atattatgta tctatataat atatatatta 2760 tatgtatatt atgtatctat ataatatata taatgtatat agatatatta tatattatgt 2820 atatatatta tgtatctatt ttatatataa tgtatataga tatacaatat atattatgta 2880 cataatatat tacatattat gtatatatac ataatatata atatattatg tatataca 3000 tgtatatata ttacatatat tatgtgtata tatattatac ataatatata tactacatta 3180

# SEL PCT 012.ST25 3191

tacataatat g

<210> 181

<211> 314

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(314)

<223> MAR of chromosome 2 genomic contig; 728676..728989

<400> 181

tgtgtatata tgtatatata atatatatta tataatatgc atatgtataa aatatgtata 60

ttatatatgt atattttata tatatgtata tattatatgt atattttata tatgtatatt 120

ttatatatat gtatatata tatatgtata ttttatatat atgtatatat tatatgtata 180

ttttatatat atgtatatat tatatatgta tattttatat atatgtatat attatatatg 240

tatattttat atatatgtat attttatata tatgtatatc atatatatgt atatattata 300

tatatgtata tctt 314

<210> 182

<211> 423

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

# **SEL PCT 012.ST25**

423

<222> (1)..(423)

<223> MAR of chromosome 2 genomic contig; 737493..737915

<210> 183

att

<211> 724

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(724)

<223> MAR of chromosome 2 genomic contig; 1069556..1070279

<400> 183

tattataata tattatatac attatattgt atatatacta tatatggtat atatagtata 60 cataatataa aatgtatatt gtaatataca ttatatatat acatagtgta cattatataa 120

# **SEL PCT 012.ST25**

180 tatataatgt atattataat gtattatata gtataatata atataatata cattatatag 240 tattgcatta tatatgctat ataatatata atatattatg tatatataca ttatatatac 300 360 tacaatatat aatgtatatt atatagtatg tataatgtaa tacattatac atagtacata 420 aagtatatta taatatatta taatatataa tatacattat atattataat gtatataata 480 tattgtatat atactatata taatgtatat acaattatat ataattgtat atatacatgt 540 atatgtatat gtatatac atgtatatgt atgtgtatat atacatatat gtatatgtat 600 gtgtatatat gtatatgtat atatgtatat gtatacgtat atatgtatat acaatgtata 660 tataatgtat ataaaaatat ataatatata caatatgtat ataatgtata taattatata 720 atat 724

<210> 184

<211> 383

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(383)

<223> MAR of chromosome 2 genomic contig; 2719918..2720300

<400> 184

# **SEL PCT 012.ST25**

<210> 185

<211> 309

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(309)

<223> MAR of chromosome 2 genomic contig; 4994249..4994557

<400> 185

<210> 186

<211> 740

<212> DNA

<213> Homo sapiens

# **SEL PCT 012.ST25**

<220>

<221> misc binding

<222> (1)..(740)

<223> MAR of chromosome 2 genomic contig; 5034916..5035655

<400> 186

60 ataattatat ataattatat aaaatataat atagaatatc taataatgta taatatataa 120 180 acataattat taattatat taattaatat ataatatat ttatacataa ttatcaatta 300 360 ataatatatc ttatacataa tatatataa tatattatat ataatatata ttatatataa 420 480 tatattttat atacaatatg atatataata taatttatat attatatata tttatatata 540 attattatat aaattatata aatataaatt atatatttat atataattat tatataaatc 600 660 tattctatat aaataatata acatatattt tatatagaat attatatata atataatata 720 tattttatat agaatattat 740

<210> 187

<211> 847

<212> DNA

#### **SEL PCT 012.ST25**

<220>

<221> misc binding

<222> (1)..(847)

<223> MAR of chromosome 2 genomic contig; 6074678..6075524

<400> 187 aatatagaca taaatatata tgcataaata tatatatgca taaatatata taaaaatata 60 120 180 cataaatata tatgtataaa tatatataca cataaatata tgtatgaata tatatacata 240 aatatatatg tataaatata tatacataaa tatataaaga tatatacata aatatatata 300 360 420 aatatataaa tatatatata aatatata aatatataaa tatatatata aatatatata 480 540 tatataaata tatataaata tataaatata tatataaata tatataaata tataaatata 600 tatataaata tataaatata taaatatata tataaatata taaatatata taaatatata 660 taaatatata aatatatata aatatatata aatatataaa tatataaa tatatataa 720 tatataaa tatataaata tatataaata tatataaata tatataaata tatataaata 780 tataaatata tatataaata taaatatata taaatatata aatatatata taaatatata 840 taaatat 847

<210> 188

<211> 784

<212> DNA

#### **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(784)

<223> MAR of chromosome 2 genomic contig; 6108986..6109769

<400> 188

60 120 180 240 atataatata atatatata tatatata tatataatat aatatatat atatatatat 300 360 420 480 540 tataatatat ataatatata ttatatataa aatatatttt atgtataata tatattatat 600 ataatatata atgtatattt atatataaaa tatatattta tatacaatgt atatttatat 660 ataaaatata tatttatata caatgtatat ttatataaat atgtgtttaa tatatgaaat 720 atatattat atataatata tatttaatct ataaaatata tattaaatat atatttatat ttaa 784

<210> 189

<211> 381

<212> DNA

# **SEL PCT 012.ST25**

<220>

<221> misc\_binding

<222> (1)..(381)

<223> MAR of chromosome 2 genomic contig; 10389032..10389412

<400> 189

tatatagagt atatatgtat a

381

<210> 190

<211> 507

<212> DNA

<213> Homo sapiens

<220>

<221> misc difference

<222> (1)..(507)

<223> MAR of chromosome 2 genomic contig; 11097807..11098313

<400> 190

#### **SEL PCT 012.ST25**

aattatatat aatttattat atataatttt atatttataa tattttata tacatatttt 60 120 180 240 300 ataataatat attatacata atttatatat aatttttata taattatata tatttatata 360 tttttatata attatatata tttatatatt tttatataat tatatattt tatatatttt 420 480 ttataaaata tataattata tataatt 507

<210> 191

<211> 329

<212> DNA

<213> Homo sapiens

<220> .

<221> misc\_binding

<222> (1)..(329)

<223> MAR of chromosome 2 genomic contig; 11234628..11234956

<400> 191

# **SEL PCT 012.ST25**

# tacagttaaa tatattaata tataatagt

329

<210> 192

<211> 584

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(584)

<223> MAR of chromosome 2 genomic contig; 797844..798427

<400> 192

tattatttta tgttataaat agataaaaat atatactaat atatatgtac ttatatatac 60 atcaatatat aatgtattat tttatactaa cgtatattat atatactagt atataatcta 120 tattatttta tatgitataa atatataata aaatatataa atattitatg catatattaa 180 tatataatat atactaacat gctaatttat atatacttat atataattta tatagtatat 240 aatatataaa tgtatataat acataattta tatattata tattaatagt ttatatatta 300 360 tagtacataa tatatattat atagttaaat aactatgtaa ctataatata taactatata 420 tgatatacag ttatatataa tataaatttt acatacagta tataaattat atactataca 480 tttatataca tatggtatat aaattatata ctatacattt atatacatat ggtatataaa 540 ttgtatacta tataatgtgt attagtatat atactaatat atac 584

<210> 193

<211> 363

<212> DNA

# **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(363)

<223> MAR of chromosome 2 genomic contig; 1093824..1094186

<400> 193

<210> 194

<211> 545

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(545)

<223> MAR of chromosome 2 genomic contig; 3456187..3456731

# **SEL PCT 012.ST25**

<4	$\Omega$	)>	1	94
_	ı jı	,-		

60 120 attataatat attatattat aatatatat atattataa atatatata atatatata 180 240 300 ttacaatata tattataaat atatatata tattataaat atatatttt atattacaat 360 420 tatatgatat attatatta atatattata taacataata tataatata aatatattaa 540 tataa 545

<210> 195

<211> 356

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(356)

<223> MAR of chromosome 2 genomic contig; 5O01567..5001922

<400> 195

#### **SEL PCT 012.ST25**

<210> 196

<211> 321

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(321)

<223> MAR of chromosome 2 genomic contig; 5457330..5457650

<400> 196

<210> 197

<211> 361

<212> DNA

# **SEL PCT 012.ST25**

361

<220>

<221> misc\_binding

<222> (1)..(361)

<223> MAR of chromosome 2 genomic contig; 8124469..8124829

<400> 197

<210> 198

t

<211> 418

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(418)

<223> MAR of chromosome 2 genomic contig; 11151485..11151902

<400> 198

atgtaactat atatatagta tatatagtat atatatacta tatagtgtgt atatatagta 60

# SEL PCT 012.ST25

<210> 199

<211> 394

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(394)

<223> MAR of chromosome 2 genomic contig; 13591477..13591870

<400> 199

<210> 200

#### **SEL PCT 012.ST25**

<211> 1194

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1194)

<223> MAR of chromosome 2 genomic contig; 14996824..14998017

<400> 200

taatatttat atatacatat aaaatttata tataatatat aatatttata tatacatata 60 aaatttatat atatataa tatttatata tacatataaa atttatatat aatatataat 120 atttatatat acatataaaa tttatatata atatataata tttatatata catataaaat 180 ttatatataa taaatatta tatatacata taaaatttat atataattta tatataacat 240 ataatatta tatataaaat ttatatataa catatatta tatataattt atataaca 300 tataatattt atataata tatatttatt tatacaattt atatataata tataatactt 360 atatatacat acataattta tatgatatat attatatata taatttatat gatatataat 420 atatctaata tatattatat atattatata tattatata aatttatata atatatata 480 540 tatataattt atataatata tattatatat ataatttata taatatatat tatatatat 600 atttatataa tatatattat atataattta tatataacat attttatata catatataat 660 ttatatataa tatatatta catatacata tataattttt atataatata aaatatttct 720 atatacatat ataatttta tataatataa aatatttcta tatacatata taatttttat 780 ataatatata tttctatata catgtctaat ttttatataa tatatatttc tatatacata 840 

# **SEL PCT 012.ST25**

acatatacat atataattt tatataatat atatttatat atacatatat aatttttaca 960
taatatatat tatatataca tatataattt atatacaaca tataatatat acatatataa 1020
tttatataca acatataata tttatgtata catatataat gtatacacaa tatataatat 1080
ttatatatac atatataatt tatatgtaat atatacatat ataatttata tgtaatatat 1140
atacatgtat aatttatatg tagtatatat acatgtataa tttatatgta gtat 1194

<210> 201

<211> 487

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(487)

<223> MAR of chromosome 2 genomic contig; 14998429..14998915

<400> 201

tagtatacat ttacacatac atgtataatt atatgtaata tataatattt acatatataa 60 ttatagataa tatatatta catatacata tataattata tataatatat aatgtttaca 120 tatacataca taattatata taatatatat ttaaatatac atatacaatt atataata 180 tatatttaca tatgcatata taattataga taatatatat ttacatatac atatataatt 240 300 tacatataca attatatata atatatattt acatatgcat atataattat agataatata 360 tatttacata tacatatata attatatata atatataata tttacatata catatataat 420 480 tatatta 487

# **SEL PCT 012.ST25**

<210> 202

<211> 421

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(421)

<223> MAR of chromosome 2 genomic contig; 16562490..16562910

<400> 202

<210> 203

t

<211> 479

<212> DNA

<213> Homo sapiens

<220>

421

# **SEL PCT 012.ST25**

<221> misc\_binding

<222> (1)..(479)

<223> MAR of chromosome 2 genomic contig; 21592301..21592779

<400> 203

<210> 204

<211> 870

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(870)

<223> MAR of chromosome 2 genomic contig; 22557584..22558453

<400> 204

tataatatat aatatacata atatgtatat tttatacaca atataaataa tatacataac 60

### **SEL PCT 012.ST25**

atatttata tataatatat atattgtata taataatata taatatatta tattatatat 180 aatatatata atatatata aaatatatat tatatataat atgtataata tataatattt tatatataat atgtataata tatattttat atataataat atgtacaata tatattttat 300 atataataat atgtacaata tatattttat atataataat atgtacaata tatattttat 360 420 480 540 600 660 720 780 840 tatatataat atataatata taatataa 870

<210> 205

<211> 1086

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(1086)

<223> MAR of chromosome 2 genomic contig; 30591960..30593045

<400> 205

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# **SEL PCT 012.ST25**

gtatatataa tatatattat attatgttat atattatgta gactatgtat taaatatatg 60 120 aatatattt totaaatatt tatatattat atattatato taatgatata taataaatat 180 atatattata tattatatat tttatatata ctatatta tatagtatat attttatata 300 tactatatat tatatattat atattttata tatactatat attatatatt atatatttta 360 420 tttatatata ctatatacta tttattatat attttatata tactatatat tatatattat 480 atattttata tataatatat atttatata tattttatat attatatata tatatata 600 atatattatc atatgtaata atagatataa tatgtaatat ataaattata attatatatt ttaatatatt aaatattatg tattaaatat atataatata tttataaata ttttatatat aatatataca tatattaaca tatatgtata tatgtatata ttatatataa cattatatat attatgttac atatactata ttttatatgt tacatatact atatattata tgttacatat 1020 aatatatata acatatatta taatatgtaa catattatat ataacatata atatatagta 1080 tatata 1086

<210> 206

<211> 406

<212> DNA

<213> Homo sapiens

<220>

# **SEL PCT 012.ST25**

<221> misc\_binding

<222> (1)..(406)

<223> MAR of chromosome 2 genomic contig; 36233909..36234314

<400> 206

<210> 207

<211> 797

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(797)

<223> MAR of chromosome 2 genomic contig; 36271745..36272541

<400> 207

# **SEL PCT 012.ST25**

acacataaac atattacata catatacaaa ttatacacat atacatatat acatatatgt 180 atatacatac attatatata aatatatgta tataaaatgt acattatata tacatatata 240 ttatgtataa ataatatata aaataaacat aatatatat tatagatatg atatatataa 300 tatatatgta tacatatata catatatgta tatataatgt acattataca tacataaaca 360 420 480 tactatatat actgtatata atatataata taatatatac tatatatact aaatataata 540 tacataatat aatatatact atatataata tataatatat aatatagtat atatactata 600 tataataatt acatattata tattatacat tatatattat ataattatta tatataatta 660 tatattacat actitigitata taatigtaaat atacattaga atatataatig tatatatatig 720 tacatatata atgtatatat gtatacatta tataaactat atataaacat tatattatat 780 aaacattata tataaac 797

<210> 208

<211> 423

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(423)

<223> MAR of chromosome 2 genomic contig; 36498521..36498943

<400> 208

tattatatta tatatttaat attatatatt taatatatta tatatttaat attatatatt 60

taatatatta tatattaat attatatat taatatata tatattaat attatata 120

#### **SEL PCT 012.ST25**

<210> 209

<211> 304

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(304)

<223> MAR of chromosome 2 genomic contig; 37179891..37180194

<400> 209

gtgtatatat atcatatata ttatatcata tatatgtgta tatatatcat atattatatc 60
atatatatgt gtatatatat catatatata tcatatatgt gtatatatca tatatattat 120
atatcatata tgtgtatata tatcatatat tatatatcat atatatgtgt atatatcata 180
tatattatat atatctcata tgtgtatata tatcatatat aatatatatg tgtatatatc 240
atatatcata tataacatat atatgtgtat atatcatata tataacatat atcatatatg 300
tgta 304

<210> 210

<211> 693

#### **SEL PCT 012.ST25**

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(693)

<223> MAR of chromosome 2 genomic contig; 38440448..38441140

<400> 210

tatatattct tttatatatt atatataata tatattcttt tatatattat atatagtata 60 tattctttta tatattatat atagtatata ttcttttata tattatatat agtatatatt 120 cttttatata ttatatatag tatatattct tttatatatt atatatagta tatattcttt 180 240 300 ttatatatca totatata atatacaaaa tatatataga ttttatatat agattattac 360 ataatagaat atattatata ttatatataa tatatacata atatataata ttatatatga 420 tataatatat atcatatata tcatataata tatattatat atcatatatt atataaata 480 540 acaaaatcta tatataatat atattatatt atatataata tacataacta tataaaaaat 660 ataatatata atatatata tatataatat ata 693

<210> 211

<211> 471

<212> DNA

<213> Homo sapiens

## **SEL PCT 012.ST25**

<220>

<221> misc binding

<222> (1)..(471)

<223> MAR of chromosome 2 genomic contig; 38887582..38888052

<400> 211

<210> 212

<211> 1221

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(1221)

<223> MAR of chromosome 2 genomic contig; 43885944..43887164

#### **SEL PCT 012.ST25**

<400> 212

60 catataaaca tatattatat gtaacatata aacatattat atgtaacata taatatataa tatataaaca tatattttat atattatatg ttacatataa tatataatat ataaacatat 120 180 attatatatt atatgtaaca tataatatat aatatataaa catatattt atatataata tataaacata ttttatatat aatatataaa catattttat atataatata taaacatata 240 ttttatatat aatatataaa catattttat atataatata taaacatata ttttatataa 300 tatataaaca tataatatat ataatatata aaagtatata atataaatat atataatata 360 420 aacatatata atataaatat atataaaata taaacatatg taatatataa acatatatta tatataatat ataaacatat attatacgta caatatataa acatatattg tacgtacaat 480 atataaacat atattatacg tacaatatat aaacatatat tatacgtaca atatataaac 540 atatattata cgtacaatat ataaacatat attatacgta caatatataa acatatatta 600 tacgtacaat atataaacat atattatacg tacaatatat aaacatatat tatacgtaca 660 atatataaac atatattata cgtacaatat ataaacatat attatacgta caataaacat 720 780 atattatacg tacaatatat aaacatatat tatacgtaca atatataaac atatattata cgtacaatat ataaacatat attgtacgta caatatataa acatatatta tatgtataat 840 atataaacat ataatata atatatatta tatatatgtt tattatatat gtttatatat tatatataac atatattatt atattatata tgtttatata ttatatatta tataatatat 960 atgtttatat attatatatt atataatata tatgtttata tattatatat tatataatat 1020 atatatgttt atatattata tattatataa tatatatgtt tatatattat atattatata 1140 taaacttaca tattttatta a 1221

<210> 213

<211> 543

<212> DNA

## **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(543)

<223> MAR of chromosome 2 genomic contig; 45818200.,45818742

<400> 213

tatgtatata tacatatata tttatacatg tatatatgta tatatacata tatatttata 60 catgtatata tatacatata tatttataca tgtatatata tacatatata tttatacatg 120 tatatatata catatatatt tatacatgta tgtatatata catatatatt tatacatgta 180 tgtatatata catatatatt tatacatgta tgtatatata catatatatt tatacatgta 240 tgtatatata catatatatt tatacatgta tgtatatata catatatatt tatacatgta 300 tgtatatata catatatatt tatacatgta tgtatatata catatatatt tatacatgta 360 tgtatatata catatatatt tatacatgta tgtatatata catatatatt tatacatgta 420 tgtatatata catgtatatt tatacatgta tgtatatata catgtatatt tatacatgta 480 tgtatatata catgtatatt tatacatgta tgtatatata catgtatatt tatacatgta 540 tac 543

<210> 214

<211> 463

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

#### **SEL PCT 012.ST25**

<222> (1)..(463)

<223> MAR of chromosome 2 genomic contig; 47055478..47055940

<400> 214 atacatacat atatacatat atacacatat atacatataa tacacacata tttacatata 60 tacacacata tatacatata tacatatata cacatatata catgcataca catatataca 120 tatatacaca catatacaca catatataca tatatacaca tatatacaca tatacacata 180 tatacacaca tatacatata tacacatata tacatatata catatataca cacatataca 240 catatataca tatacacata tatacacata tacatatata cacatatata cacatatata 300 catatataca catatataca tatatacaca tatatacaca catatacaca tatatacata 360 tatacatatg tatacacata tatacatatg tatacacata tatacacata tacatatata 420 catacacata tatacgtata tatgtgtata tatacacata tac 463

<210> 215

<211> 2482

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(2482)

<223> MAR of chromosome 2 genomic contig; 47492696..47495177

<400> 215
aatatatata aaatatatta tattotatgt aatatataga atatataaaa tatattotat 60
atattatata gaatatatat tttataatat atattattta tatatttta tatatttata 120

#### **SEL PCT 012.ST25**

ttatttatat atttatatat aatttatata atttatacat ataatttata tataatttat 180 ataaattata tatataattt atatataatt tatatataat ttatataaat tatatatata atttatatat aatttatatg atttttatat ataatttata tataatttat ataattttta 300 tatataattt atataaatt tatataattt ttatatataa tttatataat atatatatat 360 aatttatata taatttatat aatttatata tataatttat atataattta tataatttat 420 atatataatt tatataaat ttatataatt tatatatata atttatata aatttatata 480 atttatatat ataatttata cataatttat ataatttata tatataattt atataattta 540 tatatataat ttatatatat aatttatata atttatatat atgatttata taatttatat 600 atataattta tataatttat atatataaat tatatatata atttttatat aatttatata 660 tttataattt atatatttat ataatttata tatttataat ttatatattt atataattta 720 tatatttata atttatatat ttatataatt tatatataat tattcatata tttatataat 840 aattattac atatttatat atttatatat aatttatata tatttatata taatttataa 900 ataaaatata taatataa tatataatat tataatagat aaaatatata ctatatatta 960 tatattttac attatattta atattatatg tataatttta tatcatatat aatatatatg 1020 atatatataa tittatatca tatataatat atatggtata tataatitta tatcatatat 1080 aatatatatg gtatatataa ttttatatca tatataatat atgatatata attttatatc 1140 atataatata tattatatat aattttatat ctacatatta tatattatat atacaatttt 1200 atatctatct ataatatata ttatatatac aattttatat ctatataata tatattatat 1260 atacttttat attatatata aaatgtatat tatatatact tttatattat atataaaatg 1320 tttattttat atataaaatg tatattatat ataattttat tttatataaa aaatgtatat 1500 atatgtatat tatatataat tttatattat atataatatg tatattatat ataattttat 1620

#### **SEL PCT 012.ST25**

attatatata atatgtatat tatatataat tttgtattat atataatatg tatattatat 1680 atattatata taatgtatat tatataatat atattatata ttataatata taatatacat 2220 tatatatac atattatat taatatata tatattatat attacatatt atatataata 2280 aattatatat attatata aa 2482

<210> 216

<211> 539

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(539)

<223> MAR of chromosome 2 genomic contig; 47561069..47561607

## **SEL PCT 012.ST25**

aacagtaata tatcactaat atataataat atataacagt aatatatcat taatatat	aa	60
tatatcatta gtatataata ttaatatat ttaatatata atatatcata tacaatatta	120	
atatatatta atatataata atatattatt aatgtataat agtaatataa tatattatca	180	
atatatata ctaatatata ataatatatc gttaatatat aatagatcat taatatata	240	C
tgttaatata ttatgaatag ataatatatc agtatataat attaatatat taatatatta	300	
tatattattt aataatatat aatatattaa taaataat	360	
ttaatatatg actgtattat attattaata tataacaata tattatatat tatataataa	420	
tttattatat aatatataat aatatattat atattat	480	
aacattaata atatataata atgttaatat attattatat tatatattaa tatataata	539	

<210> 217

<211> 336

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(336)

<223> MAR of chromosome 2 genomic contig; 52853648..52853983

<400> 217

tatatacata aaatatatat attitatata tatacataat atatatatgt atatittatg 60
tatatatcta taatatatat aatataataa aatatacata tatatittat atatatata 120
tatacatata aaatatacat acataaaata tacatgtata tittatgtat atataatata 180
tatataaaat atacatgtat attitatata tataatatac atgtataatt aatatacatg 240

#### **SEL PCT 012.ST25**

tatgttatat atattacatg tatattatat ataatataca tataaatttt aaatttagtg 300 tatattacat gtatattata tataatatat gtatat 336

<210> 218

<211> 406

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(406)

<223> MAR of chromosome 2 genomic contig; 54866263..54866668

<400> 218

<210> 219

<211> 1452

<212> DNA

<213> Homo sapiens

#### **SEL PCT 012.ST25**

<220>

<221> misc binding

<222> (1)..(1452)

<223> MAR of chromosome 2 genomic contig; 55113305..55114756

<400> 219

ataatatata atatatatg tatattatat tattatata tatatattat taaatatata 60 120 180 tattatacta tatattatat aatatatatt atatataata atatagaata tataattata 240 tattatataa tatgtgaata atgtaatata taattatatt atttacatat tatataatat 300 ataattatat tatataatat ataattatat tattigtata ttatatataa catatacatt 360 atattatata taatataatt atatataatt aattataaat taattatata taattatata 420 atataatata taatatacat aatatataat atataataca taatatacat aatataatat 540 attatatata atatataatg ttatataatt atattatatt atataattaa ttatatgtaa 600 660 720 780 taatataata tgattatata atatattatg tatattatat attatatat gtattatgta 840 tattatatat tatatattat giatattata tattatgiat attatatat atgiatatta 960 ttatatatta tgtatattat atataaatta tattatatat tatgtatatt atatataata 1020 taaagtatat attatgtata ttatatataa tataaagtat atattatgta tattatatat 1080 aatataaagt atatattatg tatattatat ataatataaa gtatatatta tgtatattat 1140

#### **SEL PCT 012.ST25**

<210> 220

<211> 502

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(502)

<223> MAR of chromosome 2 genomic contig; 56350637..56351138

<400> 220

atatattata gaaatataaa tatatagata tatctatata ttatagaaat ataaatatat 60 agatatatct atatattata gaaatataaa tatatagata tatctatata ttatagaaat 120 ataaatatat agatatacct atatattata gaaatataaa tatatagata tacctatata 180 ttatagaaat ataaatatat agatatacct atatattata gaaatataaa tatatagata 240 tatctatata ttatagaaat ataaatatat agatatatct atatattata gaaatataaa 300 tatatagata tatctatata ttatagaaat ataaatatat agatatatct atatattata 360 gaaatataaa tatatagata tatctatata ttatagaaat ataaatatat agatatatat agatatatac 420 aacatatatg ttacatatta tatattatat atctatatat ctatataaca ttatatatct 480

# **SEL PCT 012.ST25**

#### atatatctat ataacatata ta

502

<210> 221

<211> 794

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(794)

<223> MAR of chromosome 2 genomic contig; 57051633..57052426

<400> 221

aactatatat actatattat atagttatac tatatatact atattatata gttatataac 60 tattatataa ctgtattata tagttatata actattatat aactgtatta tatagttata 120 taactattat ataactgtat tatatagtta tataactata ttatataact gtgttatata 180 gttatatatt atataactat attatataac tgtattatat agttatatat tatataacta 240 tattatata cigitattata tagitatata tiatataaci atattatata acigitattat 300 atagttatat attatataac tgtattatat agttataaaa ctatattata taactgtatt 360 atatagttat aaaactacta tataactgta ttatataatt ataaaattat actatataac 420 tgtattatat agttataaaa ctatactata taactgtatt atatagttat aaaactatac 480 tatataactg tattatatag ttataaagct atactatata actgtattat atagttatat 540 aactatacta tataactgta ttatatagtt ataaaactat actatataac tgtattatat 600 agttataaaa ttatattata taactgtatt atatagttat ataactatat tatataactg 660 tattatatag ttatataact atattatata agtgtattat atagttatat aactatatta 720 tataactgta ttatacagtt atataactat attatataac tgtattatat acttatataa 780

# SEL PCT 012.ST25 794

ctatattata taac

<210> 222

<211> 300

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(300)

<223> MAR of chromosome 2 genomic contig; 57069272..57069571

<400> 222

acacatacat atatgtatat atgcacacac atatatatgt atatatacac atacatatat 60 gtatatatac atatatgtat atacgcacat acatatatgt atatatacac gtacatatat 120 gtctctatat atacacatac acatatgtat atacatatat gtgtatatat acacaatcat 180 atatgtatat acatatatac acatatacac aaacatatat gtatatacat atatgtatat 240 acatatatac acatatacac aaacatatat gtatatacat atatgtatat acatacacaa 300

<210> 223

<211> 370

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(370)

# **SEL PCT 012.ST25**

<223> MAR of chromosome 2 genomic contig; 57235143..57235512

<210> 224

<211> 306

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(306)

<223> MAR of chromosome 2 genomic contig; 57693125..57693430

<400> 224

tacgtatata cacgtataaa tataaatata tacatgtata tacgtatata catgtataaa 60 tataaatata tatatgtata tacgtatata catgtataaa tatatatat tatatgtata 120 tatacatgta taaatatata tatatgtata tacgtatata catgtataaa tatatataca 180 tgtatatacg tatgttgtgt atacatacaa atctgtacat atatacatat atgttgtgtg 240

#### **SEL PCT 012.ST25**

tatatataca totatacatg tgtatgcgta tatatgtata tgtatatata gtatatataa 300

tacatg

306

<210> 225

<211> 500

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(500)

<223> MAR of chromosome 2 genomic contig; 59810331..59810830

<400> 225

ttiattatat gtaatatata ttgtattatt atatatatta tatataatat atattgtatt 60

tgtattatta tatatattat atataatata tattgtatat tatatattat atatattata 180

tataatatta tatattatat 500

<210> 226

<211> 565

<212> DNA

#### **SEL PCT 012.ST25**

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(565)

<223> MAR of chromosome 2 genomic contig; 59974589..59975153

<400> 226 atatatgtat aatatgtata tatgtatata ttatgtatat gttatatatg taatatatgt 60 120 acatgtatat actatgtata tattgtatat attatatatg tatatataca tatacatata 180 taatatatac atatatata tacaatatat acatgtatat tatatacgat atatacatat 240 atattatata caatatatac atagtatata aatgtataca tacatacata tatacatatt 300 360 catacgtaca tatacgtata tgtatatgca tatatgtata tatgtgcata catatatatg 420 tatatacata tatgtacata tgtacatata cgtatatatg tacatatgta catatacgta 480 tatatgtaca tatgtacata tacgtatata tgtacatatg tacatatacg tatatatgta 540 catatgtaca tatatacata tatat 565

<210> 227

<211> 427

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

# **SEL PCT 012.ST25**

<222> (1)..(427)

<223> MAR of chromosome 2 genomic contig; 60605573..60605999

<400> 227 tatataatgt atataatgga tatagatata gatatagata tatattttat ataatatata 60 120 240 atatatattt tacataatat ataatatata atacgtatta tatataatat ataatacgta 300 ttttatataa tatataatac gtattatata taatacgtat tatatattat ataatatata 360 atacgtatta tataatatac gtaattatat tttattataa tacgtattat atattatata 420 atatata 427

<210> 228

<211> 1199

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(1199)

<223> MAR of chromosome 2 genomic contig; 61229949..61231147

<400> 228

# **SEL PCT 012.ST25**

atatacatat ataaagtata tataatatat acatatataa agtatatata tcatatatac 180	1
atatataaag tatatatata atatatacat atatacatat ataaagtata tataacatat 240	)
atacatatat aaagtatata taacatatat acatatataa agtatatata taatatatac 300	)
atatatacat atataaagta tatataacat atatacatat atacagtata tataacatat 360	)
atacatatat acagtatata taacatatat acatatatac agtatatata acatatatac 420	C
atatatacag tatatataca atatatacat atatacatga agtatatata acatatatac 480	С
atatatacat gaagtatata taacatatat acatatatac atgaagtata tataacatat 540	0
atacatatat acatgaagta tatataacat atatacatat atacatatat aaagtatata 600	O
taacatatac atatatacat atataaagta taacatatac atatatacat atataaagta 66	0
tatataatat ataacatata catatataaa gtatatataa tatataacat atacatatat 720	
aaagtatata taatatataa catatacata tataaagtat atataatata	)
catatataaa gtatatataa tatatatata catatataaa gtatatataa tatatataca 840	
tatatacata tataaagtat atataatata tatacatata taaagtatat ataatatata 900	
tacatatata catatataaa gtatatataa tatataca tatatacata tataaagtat 960	
atataatata tatacatata tacatatata aagtatatat aatatatata catatataca 1020	ı
tatataaagt atatataata tatatacata tatacatata taaagtatat ataatatata 1080	
tacatatata catatataaa gtatatataa tatgtataca tatatacata tataaagtat 1140	
atataatato tatacatata tacatatata aagtatatat ataatatota tacatatat 1199	

<210> 229

<211> 454

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

#### **SEL PCT 012.ST25**

<222> (1)..(454)

<223> MAR of chromosome 2 genomic contig; 62181058..62181511

<400> 229

<210> 230

<211> 658

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(658)

<223> MAR of chromosome 2 genomic contig; 62190919..62191576

<400> 230

## **SEL PCT 012.ST25**

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taactatata tataactata tatataacta tatatata	240
ctatatatat ataactatat atataactat atatatat	300
ataactatat atataactat atatatataa ctatatata	360
atatataact atatatatat aactatatat aactatatat atataactat atatataact	420
atatatatat aactatatat ataactatat atatataact atatatat	480
ataactatat atataactat atatataact atatatat	540
atataactat atatataa ctatatatat aactatatat ataactatat atataactat	600
atatatataa ctatatatat aactatatat atataactat atatataact atatatat	658

<210> 231

<211> 1486

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(1486)

<223> MAR of chromosome 2 genomic contig; 62384127..62385612

<400> 231

# **SEL PCT 012.ST25**

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<210> 232

<211> 333

<212> DNA

<213> Homo sapiens

#### **SEL PCT 012.ST25**

333

<220>

<221> misc binding

<222> (1)..(333)

<223> MAR of chromosome 2 genomic contig; 62538649..62538981

<400> 232

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ttatatatat tatatatat ttttatatat attatatat tattttatat atatatata 180

atatatata tatatatat tatatatat attatata tatttatat atatatata 300

tatatatttt atatatatat tatatatata ttt

<210> 233

<211> 480

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(480)

<223> MAR of chromosome 2 genomic contig; 63240325..63240804

<400> 233

tatatataa atatattt tttaaatata aaatatatat atattttaat attaatata 60

#### **SEL PCT 012.ST25**

<210> 234

<211> 302

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(302)

<223> MAR of chromosome 2 genomic contig; 63935480..63935781

<400> 234

<210> 235

ta

<211> 407

#### **SEL PCT 012.ST25**

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(407)

<223> MAR of chromosome 2 genomic contig; 63935888..63936294

<400> 235

<210> 236

<211> 302

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(302)

<223> MAR of chromosome 2 genomic contig; 66958350..66958651
Seite 213

#### **SEL PCT 012.ST25**

<210> 237

<211> 651

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(651)

<223> MAR of chromosome 2 genomic contig; 68307125..68307775

<400> 237

#### **SEL PCT 012.ST25**

<210> 238

<211> 367

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(367)

<223> MAR of chromosome 2 genomic contig; 68308243..68308609

<400> 238

<210> 239

<211> 499

## **SEL PCT 012.ST25**

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

<222> (1)..(499)

<223> MAR of chromosome 2 genomic contig; 410241..410739

<400> 239

<210> 240

<211> 402

<212> DNA

<213> Homo sapiens

<220>

<221> misc\_binding

#### **SEL PCT 012.ST25**

<222> (1)..(402)

<223> MAR of chromosome 2 genomic contig; 31531..31932

<210> 241

<211> 421

<212> DNA

<213> Homo sapiens

<220>

<221> misc binding

<222> (1)..(421)

<223> MAR of chromosome 2 genomic contig; 32415..32835

<400> 241

ataaatattt tatatataat atataatata tatactatat tatatgttat atatactatt 60 ataatatata taatatata attatatatt atatatacta ttattatata tgatactatt 120 atatatata ataattatat ataatatata tattatata tatatataa tatatatata 180

# SEL PCT 012.ST25